DOCUMENT RESUME

ED 418 362 CG 028 392

TITLE	Alcohol and Health. Ninth Special Report to the U.S. Congress from the Secretary of Health and Human Services.
INSTITUTION	National Inst. on Alcohol Abuse and Alcoholism (DHHS), Rockville, MD.
REPORT NO	NIH-97-4017
PUB DATE	1997-06-00
NOTE	457p.
PUB TYPE	Information Analyses (070)
EDRS PRICE	MF01/PC19 Plus Postage.
DESCRIPTORS	*Alcohol Abuse; *Alcoholism; Behavior; Child Development; *Drinking; Economic Factors; *Fetal Alcohol Syndrome; *Health; Health Services; Literature Reviews; Mental Health; Neurology; Physical Health; Prenatal Influences; Prevention; Safety

ABSTRACT

This report provides current information on the health consequences of using alcoholic beverages and a description on current research findings on alcohol abuse and alcoholism. The focus is on research advances since September, 1993. The chapters are as follows: (1) "Epidemiology of Alcohol Use and Alcohol-Related Consequences"; (2) "Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse"; (3) "Actions of Alcohol on the Brain"; (4) "Neurobehavioral Effects of Alcohol Consumption"; (5) "Effects of Alcohol on Health and Body Systems"; (6) "Effects of Alcohol on Fetal and Postnatal Development"; (7) "Effects of Alcohol on Behavior and Safety"; (8) "Economic Aspects of Alcohol Use and Alcohol-Related Problems"; (9) "Prevention of Alcohol Problems"; (10) "Treatment of Alcoholism and Related Problems"; and (11) "Alcohol Health Services Research." Each chapter includes an extensive bibliography. (MKA)

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ED 418 362

Ninth Special Report to the U.S. Congress on

ALCOHOL AND HEALTH

From the Secretary of Health and Human Services

June 1997

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

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to the U.S. Congress on

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The tables and figures appearing on pages 5, 9, 10, 13, 14, 15, 17, 36, 37, 54, 67, 74, 77, 105, 106, 108, 112, 148, 168, 200, 206, 249, 255, 265, 310, 314, 325, 341, 342, 343, 355, 362, 377, and 381 are copyrighted and are reproduced herein with permission of the copyright holder. Further reproduction of these copyrighted materials is prohibited without specific permission of the copyright holder. All other material contained in this volume is in the public domain and may be used or reproduced without permission from the Institute or the authors. Citation of the source is appreciated.

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Foreword

The *Special Reports to the U.S. Congress on Alcohol and Health* chart our progress toward preventing and alleviating the consequences of alcohol abuse and alcoholism. Elsewhere in the introductory pages to this, the *Ninth Special Report*, you will find excellent descriptions of this progress. As a former University Chancellor, however, I wish to address not what the science is telling us, but why such findings are important. And much of the why most certainly has much to do with our Nation's youth and their ability to secure a healthy, productive future.

How many of us have been directly touched by alcohol problems? How many of us, for example, grew up with a parent's or other family member's impaired control over drinking? How many of us are faced with the loss of the potential of an adolescent whose introduction to alcohol has clouded his or her mind with alcoholic haze rather than academic and social growth? How many of us have made excuses for coworkers who we know are not performing well due to alcohol abuse or alcoholism? If you are in one of these categories, you are not alone. According to our most recent estimates, about 1 in 4 Americans are touched directly by problems caused by their own or another's drinking, and about 14 million Americans—almost 10 percent of adults—meet diagnostic criteria for alcohol abuse or alcoholism.

Alcohol misuse presents a major risk to health and social well-being throughout the life span, but youth have a special vulnerability. Alcohol is the drug most widely used by adolescents, and surveys of junior and senior high school students indicate that the vast majority have already had some experience with drinking. For some this may be one or two isolated occasions of youthful experimentation. But for others, alcohol use is excessive, places the individual in danger of immediate adverse consequences (such as accidental injury and alcohol poisoning), and may occur within a constellation of other high-risk behaviors. Moreover, for some youth a pattern of heavy drinking established in adolescence and young adulthood will continue into an adult pattern of alcohol abuse. Although recent studies show decreases in rates of alcohol use among high school seniors and in the numbers of youth who drink heavily, little change in heavy drinking has been observed among college-bound youth compared with non-college-bound youth. Finally, youthful age has been cited as one of the most important variables related to crash risk. In 1993, for example, the year of our most recent estimates, there were 5,990 traffic crash fatalities among young drivers.

These and other equally compelling findings addressed in the *Ninth Special Report* give us the "why" for alcohol research: to understand why individuals drink in ways that cause them and their loved ones harm; to understand how parental and other societal behaviors influence our youth and their decisions about alcohol; to find out how alcohol use during pregnancy can damage children throughout their lifetimes and to find the best ways to encourage expectant mothers to abstain from alcohol during pregnancy; to find out which types of community prevention programs work best for our youth and young adults; to find out how we can develop rational social and regulatory policies that act to discourage abusive drinking; and, most importantly, to find out how our loved ones can be helped toward recovery through effective intervention and treatment programs.

The alcohol research field has made progress toward answering these and other questions, and this progress is well-documented in the *Ninth Special Report to the U.S. Congress on Alcohol and Health*. These answers, along with those yet to come, will help to improve the odds for our future generations.

Donna E. Shalala
Secretary, Health and Human Services

Preface

The *First Special Report to the U.S. Congress on Alcohol and Health* was produced in 1971, barely a year after the passage of landmark legislation creating the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The greater portion of that report described, in a scant 118 pages, the entirety of what was then known about alcohol-related problems and consequences—many theories and beliefs, with little, if any, scientific evidence. Because alcohol abuse and alcoholism were seen as anything but medical problems—everything from sin to a product of poverty, to character defects, to poor child rearing—little attention was paid to developing the kind of science base that is a standard part of most other fields of medicine. The stigma attached to alcohol-related problems relegated science and the earliest scientists to second-rate status. Those scientists who undertook alcohol research 25 years ago are to be commended for recognizing the importance to our national health and well-being of building our knowledge of alcohol-related problems, and for their perseverance in conducting research that at the time was career limiting.

I am pleased to say that today, 25 years later, much has changed. One major change, of course, has been the maturing of NIAAA from a multimissioned agency to a full-fledged research Institute and partner in the National Institutes of Health (NIH) community of premiere biomedical research Institutes. The alcohol field now has access to the very best science as well as to the very best scientists, both those conducting alcohol-specific research and those whose basic research leads to greater understanding of the basic mechanism by which alcohol produces harm to the human body. I am also pleased to note that both alcohol science and the growing number of scientists who conduct alcohol-related research have achieved the well-earned respect of the medical/scientific and clinical communities. The wealth of information provided in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* and the significant number of scientists whose work is summarized and referenced in the report show conclusively that alcohol research and researchers are a vital part of the biomedical research community.

Lastly, I would note that scientific advances over the past quarter century have dramatically increased our understanding of the causes and consequences of many diseases. One of the most intriguing advances that we have seen in medical science is the growing understanding of the links between biology and behavior. That the mind and the body are linked has been posited since the early Greeks. With the cutting-edge tools available to science today, we are learning more and more about how biology and behavior influence disease and, perhaps, even more importantly, how biology influences behavior and how behavior influences biology. The linking of the biological and behavioral sciences is nowhere more evident than with respect to alcohol abuse and alcoholism. As can be seen from the comprehensive chapters of the *Ninth Special Report*, the alcohol research field is poised to take full advantage of the tools and techniques of today's science to fully explore these bio-behavioral linkages. Not only will this exploration result in the development of increasingly more potent—and effective—measures to prevent and treat these most human of problems, but it will add significantly to our overall understanding of other diseases where biology and behavior are so closely intertwined.

I commend the *Ninth Special Report to the U.S. Congress on Alcohol and Health* to your most serious attention.

Harold Varmus, M.D.
Director
National Institutes of Health

Acknowledgments

The *Ninth Special Report to the U.S. Congress on Alcohol and Health* was made possible through the hard work of many people whose cooperative efforts are reflected in the scientific accuracy and thoroughness of the document. The Editorial Review Board conceptualized the chapters, scientists recommended research articles, and both groups reviewed drafts and suggested improvements. Scientists and science writers read and summarized thousands of research articles. Science writers and editors incorporated reviewers' comments into the final document.

The result is a truly collaborative effort of scientists and science writers guided by the Editorial Review Board. Chief contributors include some of the world's most distinguished alcohol researchers and medical authorities, many of whom also contributed to previous reports.

Peer Reviewers

Bradley J. Anderson, Ph.D.
Associate Professor of Sociology
Social Science Research Center
Mississippi State University
Mississippi State, Mississippi

Mary Jane Ashley, M.D., M.Sc.
Professor
Department of Preventive Medicine and Biostatistics
Faculty of Medicine
University of Toronto
Toronto, Ontario, Canada

Thomas F. Babor, Ph.D.
Professor of Psychology
Alcohol Research Center
Department of Psychiatry
University of Connecticut Health Center
Farmington, Connecticut

Cheryl J. Cherpitel, Dr.P.H.
Senior Scientist
Alcohol Research Group
Berkeley, California

Claire D. Coles, Ph.D.
Associate Professor
Department of Psychiatry and Pediatrics
Emory University School of Medicine
Atlanta, Georgia

Ned Cooney, Ph.D.
Associate Professor
Department of Psychiatry
Yale University School of Medicine
New Haven, Connecticut

M. Lynne Cooper, Ph.D.
Associate Professor of Psychology
University of Missouri at Columbia
Columbia, Missouri

Fulton T. Crews, Ph.D.
Director
Bowles Center for Alcohol Studies
College of Medicine
University of North Carolina
Chapel Hill, North Carolina

Christopher L. Cunningham, Ph.D.
Professor
Department of Behavioral Neurosciences
Oregon Health Sciences University
Portland, Oregon

Bruce C. Dudek, Ph.D.
Professor
Department of Psychology
University at Albany, State University of New York
Albany, New York

Mary Ann Emanuele, M.D.
Professor of Medicine
Department of Endocrinology and Metabolism
Loyola University Medical Center
Chicago, Illinois

Louis Gliksman, Ph.D.
Associate Director
Addiction Research Foundation
London, Ontario, Canada

Charles Goodlett, Ph.D.
Associate Professor
Department of Psychology
Indiana University-Purdue University at Indianapolis
Indianapolis, Indiana

Deborah S. Hasin, Ph.D.
Associate Professor
Departments of Psychiatry and Public Health
Columbia University
New York, New York

Andrew C. Heath, D. Phil.
Associate Professor of Psychology and Genetics
Department of Psychiatry
Washington University School of Medicine
St. Louis, Missouri

John E. Helzer, M.D.
Professor
Department of Psychiatry
University of Vermont School of Medicine
Burlington, Vermont

Constance M. Horgan, Sc.D.
Research Professor and Director
Health Services Research
Institute for Health Policy
Heller School
Brandeis University
Waltham, Massachusetts

Thomas J. Jerrells, Ph.D.
Professor
Department of Pharmaceutical Sciences and Toxicology
Washington State University
Pullman, Washington

Thomas E. Johnson, Ph.D.
Associate Professor
Institute of Behavioral Genetics
University of Colorado
Boulder, Colorado

Donald Kenkel, Ph.D.
Associate Professor
Consumer Economics and Housing
Cornell University
Ithaca, New York

Jacqueline J. Maher, M.D.
Associate Professor of Medicine
Liver Center Laboratory
University of California at San Francisco
San Francisco, California

Willard G. Manning, Jr., Ph.D.
Professor
Institute for Health Services Research
University of Minnesota
Minneapolis, Minnesota

Tom McLellan, Ph.D.
University of Pennsylvania
Center for Studies of Substance Abuse
Philadelphia Veterans Affairs Medical Center
Philadelphia, Pennsylvania

Stephanie S. O'Malley, Ph.D.
Associate Professor of Psychiatry
Substance Abuse Treatment Unit
Yale University Schoool of Medicine
New Haven, Connecticut

Adolf Pfefferbaum, M.D.
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Stanford University School of Medicine
Palo Alto, California

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San Diego, California

Paul Roman, Ph.D.
Professor of Sociology
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Center for Research on Deviant and Behavioral Health
Institute for Behavioral Research
University of Georgia
Athens, Georgia

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Professor of Psychology and Medical Genetics
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Indiana University
Bloomington, Indiana

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Study Director
Prevention Research Center
Berkeley, California

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Professor
Department of Physiology and Pharmacology
Bowman Gray School of Medicine
Winston-Salem, North Carolina

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Cardiac Surgery Research Laboratory
University of California School of Medicine
Davis, California

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Kenneth R. Warren, Ph.D.
Director
Office of Scientific Affairs
National Institute on Alcohol Abuse and Alcoholism
Rockville, Maryland

Sharon C. Wilsnack, Ph.D.
Professor
Department of Neuroscience
University of North Dakota School of Medicine
Grand Forks, North Dakota

Writers

Thomas M. Badger, Ph.D.
Professor
Department of Pediatrics
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Marlene Oscar Berman, Ph.D.
Professor of Psychiatry and Neurology
Laboratory of Neuropsychology
Boston University School of Medicine
Boston, Massachusetts

Michael E. Charness, M.D.
Associate Professor of Neurology
Harvard Medical School
Veterans Affairs Medical Center
West Roxbury, Massachusetts

Denise L. Evert, Ph.D.
Research Associate
Department of Psychiatry
Harvard Medical School
Boston, Massachusetts

Samuel F. French, M.D.
Chief, Anatomic Pathology
Department of Pathology
UCLA School of Medicine
Harbor-UCLA Medical Center
Torrance, California

Thomas K. Greenfield, Ph.D.
Senior Scientist
Alcohol Research Group
Berkeley, California

John H. Hannigan, Ph.D.
Associate Professor
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Detroit, Michigan

William B. Hansen
Associate Professor
Department of Public Health Sciences
The Bowman Gray School of Medicine
Winston-Salem, North Carolina

Sandra W. Jacobson, Ph.D.
Research Professor
Department of Psychology
Wayne State University
Detroit, Michigan

Michael D. Klitzner, Ph.D.
Principal Social Scientist
CDM Group Inc.
Bethesda, Maryland

Jacquelyn J. Maher, M.D
Associate Professor of Medicine
Liver Center Laboratory
University of California at San Francisco
San Francisco, California

Mary E. McCaul, Ph.D.
Associate Professor
Francis Scott Key Medical Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Matt McGue, Ph.D.
Professor of Psychology
Department of Psychology
University of Minnesota
Minneapolis, Minnesota

Lorraine T. Midanik, Ph.D.
Associate Professor
School of Social Welfare
University of California at Berkeley
Berkeley, California

John Mullahy, Ph.D.
Visiting Assistant Professor of Psychiatry
Alcohol Research Center
University of Connecticut Health Center
Farmington, Connecticut

Tamara J. Philips, Ph.D.
Associate Professor
Veterans Affairs Medical Center Research
Portland, Oregon

Martha Sanchez-Craig, Ph.D.
Senior Scientist
Addiction Research Foundation
Toronto, Ontario, Canada

Lee Strunin, Ph.D.
Associate Professor
Social and Behavioral Sciences Department
Boston University School of Public Health in the School of Medicine
Boston, Massachusetts

Andrew P. Thomas, Ph.D.
Professor
Department of Anatomy, Pathology and Cell Biology
Jefferson Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania

Traci L. Toomey, Ph.D.
Research Associate
Division of Epidemiology
University of Minnesota
Minneapolis, Minnesota

Alexander C. Wagenaar, Ph.D.
Associate Professor
Division of Epidemiology
School of Public Health
University of Minnesota
Minneapolis, Minnesota

Constance Weisner, Dr.P.H.
Senior Scientist
Alcohol Research Group
Western Consortium of Public Health
Berkeley, California

Friedbert Weiss, Ph.D.
Associate Member
Department of Neuropharmacology
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D. Adrian Wilkinson, D.Phil.
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Mensana Corporation
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The report was edited and produced by Cygnus Corporation under contract number N01AA53002. Special recognition is given to Cygnus staff members **Eve Wilson, Ph.D.**, **Ellen C. Dreyer, R.N., M.S.**, and **Patti Schwartz**.

Special Acknowledgments

Several NIAAA staff members, listed below, deserve special recognition and thanks for the considerable time and effort they contributed to writing portions of the *Ninth Special Report.* Their talent, expertise, and commitment helped to ensure the document's accuracy and utility.

John Allen, Ph.D.
Chief, Treatment Research Branch
Division of Clinical and Prevention Research

Gregory Bloss, M.A.
Office of Policy Analysis

Brenda Hewitt
Special Assistant to the Director

Robert Huebner, Ph.D.
Health Services Research Program
Division of Clinical and Prevention Research

Jane Lockmuller, M.S.
Office of Scientific Affairs

Antonio Noronha, Ph.D.
Office of Scientific Affairs

Barbara Smothers, Ph.D.
Division of Biometry and Epidemiology

In addition, a number of NIAAA staff members provided technical reviews and offered helpful insights to improve the readability and usefulness of material in this report. Their efforts were instrumental in maintaining a high level of quality throughout the document. Finally, the contributions of **Kenneth Warren, Ph.D.**, Director, Office of Scientific Affairs, and **Jane Lockmuller, M.S.**, Office of Scientific Affairs, merit special recognition. Dr. Warren ably guided the overall direction and preparation of the report. Ms. Lockmuller served as managing editor of the report, overseeing all aspects of its development and review, as well as writing and editing substantial sections.

Introduction

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has just concluded a yearlong celebration of its 25th Anniversary. During the past year, we have taken time on numerous occasions and before numerous audiences to reflect on where we were 25 years ago, where we are now, and where we are going. This odyssey of reflection has made us both proud of our accomplishments and hopeful for the future.

The field has changed dramatically over NIAAA's 25-year history. It has grown significantly larger, is more science-based and professional, and enjoys greater acceptance by the general public of the need to understand, prevent, and treat alcohol-related problems. These changes can be seen in how the field conducts its daily business. The changes are reflected in the growing number of physicians' and primary health care organizations, for example, who are providing information to their memberships about identifying alcohol abuse and alcoholism among patients and making appropriate referrals. They are reflected in the extensive research effort underpinning new diagnostic classification systems, both nationally and internationally. They are reflected in the increasing attention to licensure and certification by professional organizations and States. Changes also are reflected in the growing recognition in the alcohol field of the need for increased attention to research, a recognition stemming from demands by managed care organizations, other third-party insurers, State funding agencies, and by the United States Congress for the same type of safety and efficacy evidence for alcoholism that is required for all other illnesses.

As we move toward an ever more sophisticated understanding of alcohol's far-reaching effects on individuals and society, we recognize that much of what we accept today as standard in our thinking about the basic mechanisms of alcohol-related problems and how to effectively prevent, diagnose, and treat them was little more than a collection of vague hypotheses and "hunches" 25 years ago. Today, we know that genetics plays a role in the development of alcoholism, that alcohol affects multiple receptors in the brain, and that alcohol consumed during pregnancy can have deleterious—often severe—effects on the fetus. We also have a better understanding of the cardio-protective benefits of moderate alcohol consumption, of the effects of laws and other regulatory actions on alcohol consumption and how these can help prevent alcohol-related problems, and of the effectiveness of various therapies—including pharmacotherapies—in treating alcoholism.

Each of these and other equally valuable additions to our knowledge of alcohol-related problems have stemmed from a group of "major conceptual advances" in alcoholism research. One such advance is the clear demonstration that a portion of the vulnerability to alcoholism is inherited. Although we still do not know precisely what is inherited or whether it is specific to alcohol, this conceptual advance has led to an explosion in human and animal genetic work that promises to lead to new treatments and better focused prevention efforts for those identified as most vulnerable to developing alcohol dependence. The *Ninth Special Report* addresses this important area of research in Chapter 2, "Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse."

A second conceptual advance is the application of neuroscience to understanding drinking and the phenomenon of addiction. Alcohol researchers are learning a great deal about gene proteins, second messengers, and how alcohol affects gene expression of these various substances. New imaging techniques have permitted alcohol neuroscientists to study alcohol's effects on the brain in ways not even possible just a decade ago. This conceptual advance has led to the development, among other things, of new pharmacotherapies for alcoholism treatment, such as naltrexone. These and other research developments with respect to alcohol's effects on the brain are discussed in Chapter 3, "Actions of Alcohol on the Brain."

Acceptance of the study of "mental processes" in the study of alcohol's actions is a third advance. Understanding that certain prior experiences with alcohol affect reactions to alcohol has led to two important areas of science: the issue of expectancies, where some of the actions of alcohol are produced because they are expected, not because of the pharmacology of the drug itself; and the fundamental issue of craving, that is, whether craving exists intrinsically, or whether it is dependent on cues from the environment. Chapter 4, "Neurobehavioral Effects of Alcohol Consumption," explores the progress that has been made toward discovering these and other critical biological and behavioral links in the development of alcoholism.

Another important advance has been in our understanding of how alcohol damages the body, including new understanding of withdrawal and how to safely detoxify patients, increased understanding of the mechanisms involved in alcoholic liver damage, and how alcohol damages the fetus. We also have a much better understanding of alcohol's protective effects against coronary artery disease and in possibly protecting postmenopausal women against osteoporosis. These and related issues are addressed in Chapter 5, "Effects of Alcohol on Health and Body Systems" and Chapter 6, "Effects of Alcohol on Fetal and Postnatal Development."

A fifth advance, and one that has done much to establish the credibility of alcoholism treatment within the medical establishment, has been the application of classic clinical trial techniques to alcoholism therapies (techniques such as randomization, appropriate controls, blinding, power calculations, defined and objectively measured outcomes). Related to this has been the recognition that alcoholism is a heterogeneous disease and the subsequent development of innovated research strategies to test the effectiveness of various patient/treatment matching strategies. Chapter 10, "Treatment of Alcoholism and Related Problems," explores these and other recent advances in the clinical aspects of alcohol abuse and alcoholism. Chapter 11, "Alcohol Health Services Research," explores important research areas related to how the treatment system is designed, accessed, and paid for.

Lastly, the now demonstrated fact that scientists can conduct controlled trials in prevention and that social and regulatory policies not only can be researched but that the application of research findings to policy formulation can save lives fundamentally advanced the way alcohol problems are studied and how the results of such studies are used to decrease or prevent risk. Issues involved in researching prevention strategies—whether aimed at the individual, the drinking environment, or the regulation of alcohol—are discussed in Chapter 8, "Economic Aspects of Alcohol Use and Alcohol-Related Problems," and Chapter 9, "Prevention of Alcohol Problems." Woven throughout the chapters, and introduced in Chapter 1, "Epidemiology of Alcohol Use and Alcohol-Related Consequences," are research findings that put the magnitude of alcohol-related issues into perspective.

The *Special Reports to the U.S. Congress on Alcohol and Health* document the past and provide a window to the future. By summarizing research progress every 3 years, with particular emphases on cutting-edge science, the *Special Reports* let us glimpse not only where research has been, but also where it is going. I am pleased to present this report to the United States Congress and ultimately to the American people as evidence that the 25 years of Federal support for alcohol-related research have been used both wisely and well.

Enoch Gordis, M.D.
Director
National Institute on Alcohol Abuse and Alcoholism

Overview

Section 503(a) of the Public Health Service Act, as amended, requires that the Secretary of Health and Human Services submit to the U.S. Congress a report that contains current information on the health consequences of using alcoholic beverages and a description of current research findings on alcohol abuse and alcoholism. The *Ninth Special Report to the U.S. Congress on Alcohol and Health*, prepared in accordance with the requirement, focuses on research advances since publication of the *Eighth Special Report* in September 1993.

The following overview presents some of the main highlights of the report.

Chapter 1: Epidemiology of Alcohol Use and Alcohol-Related Consequences

Alcohol epidemiology describes and explains the distribution of alcohol use, abuse, and dependence, and associated health and social consequences. Using surveillance data gathered from alcohol sales information, U.S. vital statistics, and hospital records, alcohol epidemiologists track alcohol consumption and the problems that can occur with drinking. Population-based survey studies examine the context, volume, and specific patterns that lead to particular alcohol-related problems. The knowledge gained from epidemiology studies can serve two purposes. First, it provides a foundation for monitoring health, developing and evaluating prevention and treatment approaches for alcohol use problems, and establishing alcohol-related social policies. Second, it serves as a basis for future studies exploring mechanisms that may explain data observations.

In recent years, the alcohol field has witnessed an evolution of definitions, concepts, and diagnostic criteria for alcohol use problems that has played an integral role in epidemiologic research. One major diagnostic system is the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), established by the American Psychiatric Association. The most recent version of the DSM, the fourth edition (DSM-IV), defines alcohol dependence as a cluster of cognitive, behavioral, and physiologic symptoms which indicate that a person continues to drink despite significant alcohol-related problems. Alcohol abuse is characterized as repetitive patterns of drinking in harmful situations with adverse consequences, including impaired ability to fulfill responsibilities or negative effects on social/interpersonal functioning and health. Alcohol-related consequences refers not to a specific diagnostic category but to a wide range of alcohol-related problems, including difficulties with family and friends, work problems, legal troubles, accidents and casualties, and health consequences.

Epidemiologic data have revealed a downward trend in overall per capita alcohol consumption that began in the early 1980s and continued through 1993. In 1993, per capita consumption dropped to 2.25 gallons of alcohol, the lowest level recorded since 1964. Studies suggest that several factors may have contributed to the decrease in per capita consumption, including less tolerant national attitudes toward drinking, increased societal and legal pressures and actions against drinking and driving, and increased health concerns in Americans.

National survey data also show overall increases in abstention rates, decreases in rates of heavier drinking, and related shifts in consumption patterns. These trends suggest progress. Nonetheless, alcohol-related morbidity and mortality remain significant problems in this country. For example, 14,255 persons died in alcohol traffic crashes in 1993. Young drivers, however, continue to be overrepresented in drinking driver deaths. In 1993, persons aged 16 to 24 years accounted for 28 percent of all drinking driver deaths but represented only 15 percent of all licensed drivers in the United States.

Cirrhosis mortality also continues to be a significant problem. In 1992, 25,407 persons died from cirrhosis in the United States, making it the 11th leading cause of death. Cirrhosis death rates have steadily decreased for both women and men and for whites and blacks since 1973. However, cirrhosis death rates remain markedly higher for blacks than for whites. For persons 75 years and older, death rates from cirrhosis increased between 1970 and 1992. Increases or changes in treatment for alcohol problems and improvements in prevention and nutrition may account for the general decline in cirrhosis mortality.

Hospital discharge data is another measure of alcohol-related morbidity that is useful to policymakers, health care providers, and alcohol researchers. Since 1979, there has been little change in percentages of alcohol-related diagnoses among short-stay community hospital discharges; however, the number of hospital discharges with any mention of alcohol-related morbidity has increased since 1984. This increase may partly reflect a greater awareness of alcohol-related problems by health care professionals. It is important to note that hospital discharge data may represent an underestimation of the prevalence of alcohol use disorders among hospitalized persons. One study showed that discharge records for a large teaching hospital indicated that only 1.4 percent of the patients studied had a primary and 6 percent had a secondary (but no primary) alcohol-related diagnosis. However, an additional 15 percent had screened positive for an alcohol problem upon admission.

In addition to health problems, harmful drinking patterns can lead to legal, social, and job-related problems. Survey data suggest that reports of social consequences or dependence symptoms have not changed overall, despite decreases in alcohol consumption, specific drinking patterns, and liver cirrhosis mortality. However, among young persons, individuals who never married, and those not employed,[1] reports of two or more social consequences increased significantly in survey data from 1990 compared with data from 1984. Risk function analysis of U.S. and Canadian data suggests some degree of risk for harm even at lower levels of drinking, suggesting that there is no clear lower threshold of drinking at which an individual can be "completely safe" from experiencing some consequences from drinking.

Data from a large 1992 U.S. household survey indicated that approximately 7.4 percent of people sampled could be classified as having alcohol abuse, alcohol dependence, or both in the past year. This percentage represents 13,760,000 Americans and is similar to the prevalence of alcohol abuse and dependence reported in two other national surveys. The prevalence of alcohol abuse and dependence appears generally to be higher among men than among women and among younger respondents than among older age groups.

Other studies confirm that women drink less and report fewer alcohol-related problems than men do. To date, no empirical evidence supports the convergence hypothesis, which suggests that patterns of women's drinking have changed to increasingly resemble those of men. Abstention rates among women have remained stable, and rates of heavy drinking in this population have declined during the past 10 years.

Survey data indicate that rates of monthly and daily alcohol use among high school seniors, as well as the proportion of youth who drank heavily, continue to decrease. Despite this decline, alcohol use among high school and college age students remains a concern. Compared with non-college-bound youth, college students have shown less of a decline in monthly and daily use prevalence rates and little change in the proportion of heavy-drinking students. In addition, binge drinking among college students has become a widespread problem.

Among older adults, epidemiologic surveys on alcohol use show a higher proportion of abstainers and a lower proportion of heavy drinking and alcohol abuse than among younger age groups. In addition, rates of alcohol dependence are lowest for older adults. Similar to patterns observed for younger men and women, older men drink more frequently and in greater quantities than older women.

Among ethnic groups, epidemiologic research also has identified variations in rates of alcohol use and alcohol-related problems. General trends toward stability or reduction in alcohol use and alcohol-related consequences are not always reflected in studies of broadly defined ethnic groups, such as blacks and Hispanics, or more narrowly defined ethnic or cultural groups, such as specific American Indian tribes. For example, recent studies show that rates of social consequences of alcohol use and abuse may be increasing within specific ethnic groups. Researchers are attempting to identify differences between the general population and particular ethnic groups that may help maximize the potential for intervention and prevention strategies targeted at ethnic minority groups.

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[1] This category included respondents who were retired, homemakers, or not employed full time or part time.

Chapter 2: Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse

Although the determinants of drinking behavior are diverse and complex, researchers have identified the fundamental components that influence alcohol use and abuse in humans. It has been established, for example, that alcoholism runs in families and that genetic factors contribute substantially to a familial vulnerability for the disease. Geneticists now are working toward discovering the specific genes that contribute to risk for alcoholism and identifying the neurophysiologic, biological, and psychological factors that influence the relationship between gene products and drinking behavior.

Identifying the specific genes that are involved in the etiology of alcoholism would represent a major scientific breakthrough, but it is important to recognize that no gene exists with the primary function to make a person drink chronically and abusively. Genetic factors exert their influence indirectly, and knowledge of this influence must be integrated into a broader framework that considers the additional and interactive effects of individual-level factors and contextual factors that either increase or decrease the likelihood that an individual will use or abuse alcohol.

A range of genetic studies have contributed to knowledge about how predisposition for alcoholism is transmitted in families. Studies of families have revealed that first-degree relatives of alcoholics are two to seven times more likely than the general population to develop problems with alcohol sometime in their lifetime. Twin and adoption studies have confirmed that genetic determinants play an integral role in a person's increased risk for developing the disease.

Many people who are at risk for developing alcoholism, however, never develop the disease, suggesting that some factors may be protective or may render some individuals resilient. Researchers have found that high levels of parental support, close monitoring of adolescent activity by parents, and positive adolescent-parent communication may all serve to modify the effects of parental alcohol abuse on adolescent alcohol use. A parent's abusive drinking also may help to protect against the onset of alcohol problems in adolescents.

The foundation laid by family, adoption, and twin studies is being expanded upon by molecular genetic research. Scientists already have made important progress in identifying the effects of alcohol-metabolizing genes and showing how those genes influence drinking behavior among certain Asian populations. This information can provide insights into the determinants of alcohol use patterns of people at various levels of genetic risk for alcoholism, thus expanding our knowledge of the causes of alcoholism and advancing our efforts toward improved alcoholism prevention and treatment.

Genetic studies with animal models are an important component of molecular genetic research in the alcohol field. Animal studies are providing useful data that potentially can inform alcoholism studies in humans. For example, scientists are using animals to identify the location of genes responsible for the genetically influenced traits that are thought to underlie responses to alcohol. These traits are known as quantitative traits, and more than one gene influences the magnitude of each attribute. A section of DNA on a chromosome thought to influence a quantitative trait is known as a quantitative trait loci (QTL). QTL analysis enables researchers to locate and measure the effects of a single QTL on a trait, or phenotype, and ultimately to gain knowledge of the complex physiologic underpinnings of alcohol-related behavior. Recent studies are advancing knowledge in this area. For example, scientists recently identified two loci—*Alcp1* and *Alcp2*—that appear to have significant gender-specific effects on alcohol consumption in mice. Such findings suggest that preference for alcohol, a quantitative trait, may be controlled by different genetic mechanisms in males and females.

Individual-level factors also play an important role in the onset of alcohol problems. These factors are characteristics of an individual that either increase or decrease the likelihood that he or she will use or abuse alcohol. Among the various classes of individual-level factors currently being investigated are alcohol sensitivity, neurophysiologic processes (e.g., differences in event-related potentials), biochemical markers (e.g., serotonin dysfunction, monoamine oxidase activity), personality characteristics, and cognitive processes. Studies suggest that offspring of alcoholics inherit altered sensitivity to alcohol's effects, and this altered sensitivity appears to be a good predictor of who does or does not develop alcoholism. The personality dimensions of behavioral undercontrol and negative emotionality also have been found to differentiate those individuals who develop alcohol problems from those who do not.

Sociocultural and contextual factors also can influence drinking behavior. Individual attitudes about the propriety of drinking are influenced by cultural norms, and these attitudes affect whether, how much, and when a person drinks. Drinking behavior is influenced by friends' drinking behaviors, parental standards regarding drinking, and the extent to which a person has been exposed to or is experiencing severe psychological stress.

The multiple factors that can influence the development of alcohol problems can be conceptualized as falling along a pathway that links molecular studies to developmental studies. Genes control the synthesis of proteins that influence biochemical systems and neurophysiologic processes. In turn, these elements affect personality dispositions and cognitive functioning. Moreover, these biological pathways are constantly modulated by external factors. Ample research indicates that biological and nonbiological factors both influence drinking behavior and that the two types of influences are interdependent.

Chapter 3: Actions of Alcohol on the Brain

For many years, alcohol researchers have worked to define the cellular and molecular mechanisms by which alcohol produces intoxication, dependence, withdrawal, and other short- and long-term changes mediated through the central nervous system (CNS). New and powerful research tools have facilitated the study of alcohol's effects on the proteins and genes that control CNS functions. As a result, many of the neuromolecular actions of alcohol have been characterized in relation to behavioral and physiologic manifestations and changes that occur with alcohol use and abuse. These findings have provided clues toward developing new pharmacologic strategies for preventing and treating alcoholism.

Unlike other psychotropic drugs, alcohol does not act through a single receptor. Instead, alcohol interacts with and alters the activities of many different cellular components, including neurotransmitter receptors, cell membranes, intracellular signaling enzymes, and genes. As a result, alcohol may have diverse and profound effects on nerve cell function.

The chemical and structural nature of cell membranes renders them permeable to alcohol. This means that nerve cell proteins residing in the cell membrane and within the cell are vulnerable to alcohol's effects. Alcohol may act directly on these proteins to disrupt their normal functions. Alcohol also may alter the fluidity and electrical properties of membranes; with long-term alcohol exposure, significant reorganization of membrane components is observed. Changes in membrane properties may alter the shape, interactions, and functions of membrane proteins.

Among the proteins affected by alcohol are ligand-gated ion channels that serve as receptors for several neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate, serotonin, and adenosine triphosphate (ATP). GABA is the brain's major inhibitory neurotransmitter, and glutamate is the brain's major excitatory neurotransmitter. The combined actions of GABA and glutamate through their respective receptors produce short-term changes in membrane electrical potential, firing of nerve impulses, and release of many neurotransmitters. Because alcohol stimulates GABA receptor function and inhibits glutamate receptor function, the drug has the potential to influence many of these nervous system activities. Among numerous other effects, alcohol's acute actions on GABA receptors contribute to behavioral manifestations of intoxication, such as sedation, incoordination, and anxiety reduction. Alcohol-induced inhibition of glutamate receptor function produces similar behavioral effects. The actions of alcohol on glutamate receptors also may explain its effects on attention and sensory discrimination.

One type of GABA receptor, the GABA_A receptor, is widely distributed in brain tissues. However, alcohol sensitivity of GABA_A receptors is observed only in certain brain regions, perhaps because of variations in the combination of protein subunits that make up the receptor. When an enzyme known as protein kinase C (PKC) adds phosphate molecules to GABA receptors, receptor sensitivity to alcohol increases, as shown in cultured cells and in studies of mouse strains in which functional PKC genes had been deleted. Deletion of PKC in these animals abolished alcohol-induced enhancement of GABA receptor activity and also reduced alcohol-induced anesthesia. However, with chronic alcohol exposure, $GABA_A$ receptors become less responsive to alcohol stimulation, an effect that may result from changes in expression of receptor subunits. This adaptive response may play a role in the development of tolerance to alcohol's effects observed with chronic alcohol consumption.

Similar to GABA receptors, glutamate receptors may be composed of different subunit combinations and may, as a result, vary in sensitivity to alcohol. There are three types of glutamate receptors; for one type, known as the *N*-methyl-D-aspartate (NMDA) receptor, variations observed in receptor subunit combinations may explain differences in alcohol responsiveness of various brain regions. One consequence of acute alcohol exposure on NMDA receptors may be interference with brain processes critical to the consolidation of new memories; thus, NMDA receptors may play a role in alcoholic blackouts and other alcohol-associated memory disorders. With chronic alcohol exposure, numbers of NMDA receptors found in brain tissues increase. This adaptive response may compensate for the inhibition of NMDA receptor function observed with acute alcohol exposure. However, increases in NMDA receptor expression also may contribute to the development of seizures during alcohol withdrawal and may render neurons more vulnerable to cell death caused by excessive glutamate-stimulated excitation.

Other alcohol-sensitive ligand-gated ion channels include ATP receptors and a type of serotonin receptor known as the $5\text{-}HT_3$ receptor. Alcohol appears to inhibit activities of ATP receptors and enhance activities of $5\text{-}HT_3$ receptors. The $5\text{-}HT_3$ receptor has been implicated in alcohol's intoxicating and addictive properties; in addition, agents that block or reverse $5\text{-}HT_3$ receptor functions ($5\text{-}HT_3$ antagonists) can decrease craving for alcohol in humans. Although pharmacologic studies indicate that alcohol acts directly on these ligand-gated ion channels to alter their functions, the role of ATP receptors and $5\text{-}HT_3$ receptors in intoxication and other responses to alcohol requires further investigation.

Alcohol may produce intoxication and dependence in part through direct or indirect effects on opioid receptors. Treatment of cultured cells with alcohol increases the expression of one type of opioid receptor, the delta opioid receptor. In addition, alcohol stimulates nerve cell release of opioids, such as enkephalins and endorphins, in the brain. In turn, opioids bind to delta opioid receptors to promote release of the neurotransmitter dopamine in a brain structure known as the nucleus accumbens. Dopamine release is thought to mediate the euphoric and other pleasant feelings experienced with intoxication and has been implicated in alcohol's reinforcing effects—those that promote continued drinking and may lead to alcohol dependence and craving for alcohol. The opioid receptor antagonist naltrexone is thought to block dopamine release and reduces craving for alcohol in humans.

Within nerve cells, alcohol may interfere with multiple elements of signal transduction. For example, acute alcohol exposure enhances neurotransmitter-induced activity of adenylate cyclase, an enzyme that initiates a cascade of intracellular reactions essential for normal cell function. In contrast, chronic alcohol exposure may produce a broadly suppressive effect on the stimulation of adenylate cyclase by many different neurotransmitters, an adaptive process known as heterologous desensitization. The mechanisms behind alcohol-induced heterologous desensitization vary among cell types but include increases and decreases, respectively, in the inhibitory and stimulatory proteins (G proteins) that regulate adenylate cyclase activity. Alcohol-induced heterologous desensitization may counterbalance the acute stimulatory effects of the drug on adenylate cyclase and may represent a form of cellular tolerance.

The functions of PKC, another crucial participant in intracellular signaling reactions, also are influenced by alcohol. Chronic alcohol exposure may increase the abundance and activity of PKC and result in a variety of adaptive changes. For example, alcohol stimulation of PKC may enhance neurite outgrowth, a process that may contribute to alcohol-associated brain injury by disturbing the development and organization of the CNS. PKC has an extensive role in controlling many other cellular activities, including protein synthesis and the actions of various other membrane proteins. Thus, alcohol-induced alterations in PKC activity may contribute to a wide range of adaptive responses within the CNS.

Effects of alcohol on gene transcription, whereby the genetic code of DNA is copied as a part of protein synthesis, may yield some of the more enduring alcohol-associated changes in nerve cell function. Numerous alcohol-responsive genes have been identified. Among these are the genes for molecular chaperons, which regulate the trafficking of other proteins as the proteins are synthesized and inserted into different cellular compartments. Increases in the abundance of molecular chaperons may account for alcohol-induced changes observed in protein trafficking. In addition, alcohol increases transcription of the gene encoding tyrosine hydroxylase, an enzyme critical to synthesis of the neurotransmitters dopamine and norepinephrine. Investigations that characterize these and other alcohol-responsive genes will provide clues about persistent CNS changes associated with alcohol use.

By acting on many different cellular components and functions, alcohol produces diverse immediate and long-term alterations in CNS activity. Neuroscience research is expected to continue identifying and characterizing cellular targets and processes affected by alcohol. This information will help reveal the mechanisms behind alcohol-induced intoxication, tolerance, dependence, and withdrawal and may contribute to the development of pharmacologic agents that offset or alleviate harmful consequences of alcohol use and abuse.

Chapter 4: Neurobehavioral Effects of Alcohol Consumption

Our knowledge of the brain structures and functions affected by alcohol has expanded significantly in recent years. With this knowledge has come a greater understanding of the links between alcohol-induced brain changes and alcohol-induced behavioral changes.

Researchers have used sophisticated methods and animal models to study alcohol-seeking behavior and the environmental and genetic forces that motivate and reinforce drinking. Animals selectively bred for alcohol preference or nonpreference have been used in specially designed behavioral approaches such as operant models, conflict tests, and drug discrimination procedures. For example, scientists have used operant procedures, in which animals can obtain alcohol only by performing a specific task, to study the "cost" of alcohol as an environmental influence on alcohol intake. These experiments have shown that the amount of alcohol consumed can be modified by its cost, defined as the amount of work required to obtain the drug, regardless of genetic preference for alcohol. In addition, these studies have revealed an association between genetic predisposition for high alcohol intake and a greater motivation to work for alcohol.

Conflict tests, in which animals trained to respond to alcohol as a reinforcing stimulus are occasionally punished (e.g., by the administration of an electric shock), have been used to study the anxiety-reducing properties of alcohol. Conflict tests and similar behavioral strategies have shown that the stress-reducing actions of alcohol likely reinforce its continued use and contribute to the development of alcohol dependence.

Drug discrimination procedures determine the ability of animals trained to recognize alcohol to distinguish between alcohol's subjective effects (such as its anxiolytic and euphoric effects) and the effects of other psychotropic drugs. In such tests, identification of drugs that can fully or partially substitute for alcohol, together with knowledge of the neurotransmitter systems affected by those drugs, can help characterize the brain pathways that mediate the behavioral effects of alcohol. Studies using drug discrimination procedures have shown that alcohol's subjective effects are not mediated by any one neurotransmitter or neurotransmitter receptor but depend on the combined actions of multiple neurotransmitter systems.

Among the many neurotransmitters characterized as mediators of alcohol-related behaviors are dopamine, serotonin, GABA, opioids, glutamate, and a new class of compounds known as neurosteroids. Dopamine, which mediates the pleasurable effects of many drugs, has been strongly implicated in the reinforcement of alcohol-seeking behaviors. The neurotransmitter also has been implicated in the aversive effects of alcohol withdrawal. For example, alcohol-dependent animals undergoing withdrawal will self-administer alcohol in an apparent attempt to alleviate withdrawal symptoms; furthermore, alcohol restores a withdrawal-associated dopamine deficiency observed in these animals. Collectively, these findings suggest that dopamine contributes to alcohol's positive and negative reinforcing properties.

The actions of serotonin have long been associated with alcohol-seeking behavior in experimental animals and in humans. In regions of the brain implicated in drug reinforcement, selectively bred alcohol-preferring rats have reduced serotonin content and fewer serotonin neurons compared with their alcohol-nonpreferring counterparts. In humans, alcoholism is associated with a loss of serotonin neurons and deficiencies in serotonin synthesis, turnover, and receptor function. Recent investigations have characterized several serotonin receptor subtypes ($5HT_3$, $5HT_2$, and $5HT_{1A}$) as participants in the control of alcohol intake.

Receptors for the inhibitory neurotransmitter GABA are thought to play critical roles in the reinforcing actions of alcohol. Alcohol has anxiolytic effects that resemble those of benzodiazepines, agents that act through the A-type GABA receptor (GABA_A), suggesting that this pharmacologic property of alcohol is mediated through GABA_A receptors. Studies of alcohol's stress-reducing effects have implicated GABA_A receptors, in that certain GABA_A receptor antagonists—compounds that block or reverse GABA's actions at GABA_A receptors—can reverse the anxiolytic effects of alcohol in conflict tests.

Similarly, receptors for the excitatory neurotransmitter glutamate appear to participate in alcohol reinforcement. Study findings suggest that alcohol may interfere with NMDA receptor function by acting as a noncompetitive NMDA receptor antagonist.

A new line of research explores the role of neurosteroids, compounds that bind to and modulate the activity of both GABA_A receptors and NMDA receptors. Some neurosteroids produce neuronal inhibition via the GABA_A receptor to produce anxiolytic and hypnotic effects. Others act as GABA receptor antagonists to increase neuronal excitability and can thereby induce anxiety and convulsions. Different neurosteroids also can enhance or interfere with the physiologic and behavioral effects of glutamate at the NMDA receptor. Neurosteroids may interact with alcohol to influence alcohol-seeking behavior. Researchers have just begun to characterize these interactions in investigations that may aid development of novel pharmacotherapeutic agents.

Alcohol is thought to stimulate or inhibit numerous neurotransmitter activities simultaneously in producing its rewarding and reinforcing effects. For example, interactions among alcohol, serotonin, and dopamine are suggested in experiments showing that 5HT_3 antagonists can reduce alcohol intake and dopamine release in the nucleus accumbens. Similarly, alcohol produces its rewarding properties in part by activating dopamine release through actions on opioid peptides, such as endorphins and enkephalins. Naltrexone and another opiate antagonist that interacts selectively with the delta opioid receptor have been shown to prevent alcohol-induced dopamine release. Thus, the clinical efficacy of opiate antagonists may lie, in part, in their ability to block the reinforcing effects of alcohol that depend on dopaminergic mechanisms in the brain.

Chronic alcohol use may cause neuropsychological deficits in learning and memory. Alcohol appears to impair the consolidation of newly acquired information, possibly through effects on NMDA receptors that participate in long-term potentiation, a process thought to be critical to memory formation. Biochemical studies of memory deficits that occur with chronic alcohol consumption have associated these deficits with reductions in brain levels of the neurotransmitter acetylcholine. Although evidence suggests that alcohol-related memory deficits appear to involve disruption of glutamate and acetylcholine pathways, the precise mechanisms behind these deficits require further investigation.

Chapter 5: Effects of Alcohol on Health and Body Systems

Excessive alcohol consumption may have widespread deleterious effects on all tissues and organs of the body, with consequences that include neuropsychological and reproductive abnormalities and increased susceptibility to infection. Sometimes the effects of alcohol on one organ system can impair another; for example, alcoholic liver disease may lead to metabolic and other physiologic alterations that, in turn, impair central nervous system function. Adverse consequences of alcohol abuse may vary considerably, depending on factors such as the amount of alcohol consumed, gender, age, and nutritional status.

Because the liver receives portal blood directly from the intestines, it takes the brunt of high alcohol concentrations. In addition, in its role as the primary site of alcohol metabolism, the liver forms abundant toxic alcohol metabolites. As a result, liver damage may be among the most serious consequences of alcohol abuse. Heavy alcohol use may cause liver inflammation and progressive liver scarring (fibrosis or cirrhosis). Among the mechanisms thought to contribute to liver damage are the release of cytokines, which are substances with inflammatory, fibrogenic, and cell growth-promoting properties, and the formation of free radicals, which are reactive oxygen molecules that can interact with proteins, lipids and DNA, causing damage or death to liver cells. Acetaldehyde, a principal metabolite of alcohol, can form adducts by reacting with cellular proteins; the result may be direct damage to liver cells or stimulation of inflammatory autoimmune reactions in liver tissues. Acetaldehyde-protein adducts also may stimulate liver cell collagen synthesis, a process thought to contribute to fibrosis and cirrhosis. A promising approach to preventing fibrosis involves administration of polyunsaturated soybean lecithin, which may promote the breakdown of hepatic collagen.

Alcohol abuse also contributes to heart and cardiovascular disease, although light drinking appears to have some benefits for cardiac health. Heavy alcohol consumption can interfere with the mechanical functions of the heart and may cause progressive functional changes and tissue damage leading to cardiomyopathy and heart failure. Excessive alcohol consumption also is associated with high blood pressure and an increased risk for coronary artery disease and stroke. However, light to moderate drinking appears to be beneficial in preventing coronary artery disease, perhaps by elevating blood levels of high-density lipoprotein or by inhibiting clotting processes that contribute to atherosclerosis and thrombosis.

Alcohol-associated neuropsychological disorders typically involve damage to the limbic system, the diencephalon, and the frontal cerebral cortex of the brain. Among the many and diverse neuropsychological problems resulting from this damage are deficits in short-term memory, disruption of cognitive and motor functioning, reduced perceptual abilities, and emotional and personality changes. With advances in brain and functional imaging techniques and with the development of neurocognitive tests, researchers hope to identify connections between alcohol-associated structural and metabolic changes in the brain and alcohol-associated impairment in mental processes.

A variety of studies show that alcohol interferes with normal endocrine system activities. Excessive alcohol use may profoundly impair reproductive development and function in both women and men. Recent studies in women show that alcohol consumption may increase estrogen levels; this effect may be related to an observed association between alcohol consumption and increased risk for breast cancer. Chronic alcohol exposure may also alter the secretion patterns of growth hormone. Consequences of this disruption may include numerous metabolic and endocrine changes, because growth hormone regulates levels of other growth stimulators as well as alcohol- and steroid-metabolizing enzymes. In addition, alcohol withdrawal induces marked elevations in glucocorticoid stress hormones. Glucocorticoids in excess may be neurotoxic; thus, glucocorticoid elevations may contribute to the behavioral and neurological changes observed with withdrawal.

In healthy individuals, the complex network of lymphoid cells and regulatory cytokines that compose the immune system efficiently detects and eliminates potential pathogens. Alcohol consumption, particularly of a chronic or abusive nature, depresses the immune system by altering the function, regulation, and distribution of lymphoid cells. The result may be dysregulation of immune defenses and an increased susceptibility to infectious disease and cancer. Immunological abnormalities observed with long-term alcohol abuse in humans also include autoimmune processes that damage liver tissues.

Chapter 6: Effects of Alcohol on Fetal and Postnatal Development

Maternal drinking can produce a spectrum of harmful effects in exposed offspring, ranging from a characteristic pattern of gross morphological anomalies and mental impairment (including mental retardation) to more subtle cognitive and behavioral dysfunctions. Fetal alcohol syndrome (FAS) is the most severe birth defect produced by prenatal alcohol exposure; the terms "alcohol-related birth defects" (ARBD) and "fetal alcohol effects" (FAE) are used to describe individuals who exhibit some of the attributes of FAS but do not fulfill the diagnostic criteria for FAS.

Despite the existence of standardized criteria, clinicians and researchers have considerable difficulty identifying individuals with FAS, for a variety of reasons. For example, none of the characteristic abnormalities of the syndrome is specific to the diagnosis. In addition, specific facial abnormalities may be subtle and difficult to recognize, their expression may change with age, and their severity may vary among individuals and among racial and ethnic groups. Identification of individuals with ARBD or FAE, who can have behavioral and cognitive problems that persist with age, may be even more difficult than diagnosis of FAS. In response to these diagnostic challenges, researchers are exploring the use of new tools that may improve efforts to diagnose FAS. These tools include computer-assisted morphometric analysis of facial features; magnetic resonance imaging of the brain, which can reveal markers of alcohol-induced injury; and behavioral profiles of people affected by prenatal alcohol exposure.

Recent studies indicate that the deficits associated with FAS are pervasive and long lasting and have a marked effect on an individual's ability to live independently. Although many of the physical characteristics become less prominent after puberty, intellectual problems endure and behavioral, emotional, and social problems become more pronounced. Children with FAS and ARBD frequently are described as being hyperactive and impulsive and having short attention spans. Maladaptive behaviors, such as poor judgment, failure to consider the consequences of one's actions, and difficulty perceiving social cues, are common.

The relationship of quantity, frequency, timing, and pattern of maternal drinking to infant and child outcome has been addressed by prospective longitudinal studies. Findings from some, but not all, of these studies have revealed an association between prenatal alcohol exposure and growth deficits at birth; these deficits have been found to persist in infants 6 to 8 months after birth and in children 6 years of age. Prospective studies also have reported a range of behavioral and cognitive deficits in infants exposed to alcohol in utero.

Studies have yet to reveal fully how the timing of alcohol exposure, dose response, and maternal drinking patterns disrupt particular stages of development. For example, several longitudinal studies have found that first-trimester exposure to alcohol is associated with craniofacial anomalies in children. The association between timing and growth, however, is not as clear. Neurobehavioral effects seemingly are sensitive to periods of exposure during development: Studies suggest that heavy maternal alcohol use during the first and second trimesters appears to increase the occurrence of delayed language development in children.

Because it is clear that alcohol-induced birth defects are completely preventable with maternal abstinence from alcohol, prevention is a central research issue. Researchers are attempting to develop multilevel strategies that take into account the multiple factors that influence drinking in different racial, ethnic, and socioeconomic segments of society. These strategies, which ideally will interact to enhance prevention outcome, include community education programs to increase awareness of the hazards of drinking alcohol during pregnancy, approaches to effectively identify women whose drinking places them at risk for adverse pregnancy outcomes, and strategies aimed at intervening with individual women who are problem drinkers and thus at greatest risk for having a child who is affected by alcohol.

Animal models and in vitro biological systems enable researchers to conduct controlled experiments on the interaction of the complex pharmacologic, biochemical, and physiologic effects of alcohol with genetic, experiential, social, and behavioral factors that influence alcohol's effects in humans. Animal experiments have demonstrated that peak maternal blood alcohol concentration determines the likelihood and severity of alcohol-induced impairments. In addition, animal studies have demonstrated that the period(s) during pregnancy when blood alcohol concentration is high has an important influence on the variable expression of ARBD.

The consequences of alcohol exposure are similar in animals and in humans. Animal studies suggest that prenatal alcohol exposure causes poor somatic growth, malformation of major organs, craniofacial anomalies, and associated central nervous system dysfunction. Animals exposed prenatally to alcohol also exhibit neurobehavioral problems, such as hyperactivity, perseveration, poor balance and coordination, difficulty walking, and inability to learn from past experiences.

Results of studies examining how prenatal alcohol exposure injures the developing brain indicate that such exposure can produce profound anatomical changes in the fetal central nervous system by altering cell proliferation, migration, differentiation, and pruning. Dose, duration, and pattern and timing of exposure can influence the specific neuroanatomical outcomes. Alcohol also appears to have concentration and time-dependent effects on neural tube formation. Prenatal exposure may also affect the development and function of glial cells, which are "nonneural" cells in the brain that participate in a variety of normal functions. Finally, animal studies indicate that prenatal alcohol exposure affects neurotransmitter systems in the brain, including the serotonin, dopamine, acetylcholine, glutamate, and gamma-aminobutyric acid systems; the nature of the dysfunction may depend critically on when alcohol exposure occurs in development.

Studies using experimental animals and in vitro models have described the roles of acetaldehyde, retinoic acid, nerve growth factor, glucocorticoids, free radicals, and hypoxia in alcohol-induced fetal damage. Greater knowledge of the mechanisms of alcohol teratogenesis has important implications for risk assessment and the development of effective strategies for the prevention of alcohol-induced birth defects in humans.

Chapter 7: Effects of Alcohol on Behavior and Safety

Numerous studies have shown that alcohol use and abuse can have adverse effects on a wide variety of behaviors, with serious consequences for persons of all ages and backgrounds and for the health and well-being of society. Each year, more than 100,000 deaths in the United States result from alcohol-related causes. Motor vehicle crashes, falls, fires, and drownings cause more than 75 percent of deaths from unintentional injuries; alcohol use has been associated with a large percentage of deaths from these causes. Alcohol use also has been linked with high-risk sexual behavior as well as family and marital violence, homicide, and suicide.

Researchers have theorized that alcohol and injury may interact in two ways. First, the context and the place in which an individual consumes alcohol may result in an increased risk of injury. For example, drinking in bars where the risk of assault may be high increases an individual's exposure to hazardous circumstances. Second, direct biological effects of alcohol may lead to injury by interfering with perception and responsiveness to potential hazards. The consequences of alcohol's direct biological effects are apparent in the large proportion of motor vehicle-related injuries associated with alcohol.

Traffic crashes are the leading cause of death for Americans under the age of 35, and alcohol use plays a significant role in these deaths. However, the proportion of deaths from alcohol-related traffic crashes has decreased in recent years. The number of intoxicated drivers killed in traffic crashes decreased by 28 percent between 1983 and 1993, with reductions of nearly 50 percent among persons 16 to 20 years of age. Recent research suggests that raising the minimum legal drinking age to 21 has helped to reduce the proportion of alcohol-related highway crashes reported for teenagers. Between 1977 and 1993, the number of male drivers of all ages involved in fatal alcohol-related crashes dropped by 22 percent, whereas the number of female drivers involved in such crashes increased by 18 percent. However, the total number of fatal traffic crashes involving women drivers who were legally intoxicated has remained far below that of men.

Direct associations between alcohol use and other types of injury, such as those associated with aircraft crashes, fires and burns, boating accidents, and violence, are less clear. For example, although associations have been observed between alcohol use by pilots and reduced aircraft safety, these findings must be interpreted with caution because many of the data are based on individual case studies rather than on epidemiologic studies. However, simulated flight experiments clearly show that pilot planning, performance, and vigilance are impaired by acute and hangover effects of alcohol.

Available evidence suggests that alcohol use may be a significant risk factor in drownings and in other fatal or nonfatal injuries that occur on or near the water. Studies have shown that drinking can increase the risk of injury for both boat operators and boat passengers: Because alcohol can impair balance and motor coordination, a drinking passenger may be more likely to fall overboard even when the boat is being operated safely. In addition, alcohol consumption may play a significant role in diving accidents that result in spinal cord injury.

Alcohol use is thought to contribute to the risk of injuries and fatalities caused by fires and burns, in part because alcohol may increase the risk of falling asleep while smoking and may reduce awareness of smoke and fire alarms. Furthermore, drinking may affect the outcome of burn injuries, in that burn patients with positive levels of blood alcohol concentration (BAC) have been shown to have higher fatality rates than patients without detectable blood alcohol.

Research has shown that alcohol use is a factor in a significant proportion of violent and aggressive events. Data from numerous studies support a strong relationship between alcohol and various types of violence, including homicides, suicides, and spousal abuse. For example, a review of investigations examining the link between alcohol and homicide revealed that in most studies, more than 60 percent of persons who committed homicides were drinking at the time of the offense. Alcohol use also may increase the risk of becoming a victim of violence and of sustaining injury due to violence. One study has shown that emergency room patients who were injured in violent events were twice as likely to have positive BACs than were patients with injuries unrelated to violence. However, the presence of alcohol in violent episodes does not mean that alcohol itself causes violent behavior. Rather, alcohol is likely to be only one of multiple factors that interact to precipitate violent behavior in some individuals.

Finally, alcohol use is thought to play a role in many risk-taking or sensation-seeking behaviors. In particular, research has correlated drinking with high-risk sexual behaviors—those that contribute to the spread of sexually transmitted diseases such as AIDS. Understanding the role of alcohol in high-risk sexual behavior is of great concern, particularly in view of recent survey results showing that people who met diagnostic criteria for alcohol dependence or abuse or were heavy or binge drinkers had an increased risk of exposure to human immunodeficiency virus and of developing AIDS.

As for other causes of injury and death, the causal role of alcohol in high-risk sexual behavior is unclear. The paucity of information about alcohol's direct role in injuries due to high risk behaviors, violence, falls, fires, and other causes, combined with the tremendous negative impact such injuries have on individuals and on society, underscores the need for further research and improved methods for characterizing causal associations between alcohol and casualties.

Chapter 8: Economic Aspects of Alcohol Use and Alcohol-Related Problems

Research continues to illuminate the role of economic factors as determinants of alcohol consumption and of various problems that often are associated with drinking. Using standard economic models of the determinants of consumption behavior, a substantial and growing body of research has established that consumption of beer, wine, and distilled spirits declines in response to increases in the prices or taxes associated with these beverages. Early results from a new area of emphasis in this research suggest that the small proportion of drinkers with the highest consumption levels may be much less sensitive to price changes than are drinkers who consume at more moderate levels. Several studies have also found that increases in alcoholic beverage taxes and prices are associated with reductions in motor vehicle fatalities and other adverse outcomes that are frequently associated with alcohol consumption. Finally, recent studies on the role of alcohol advertising as a determinant of alcohol consumption and alcohol-related problems continue the inconsistent pattern of results found in earlier studies. Some recent studies found no significant link between advertising and consumption levels, but another recent study found significant effects of advertising on traffic fatality rates.

Another main area of recent research on economic aspects of alcohol use and abuse has examined the labor market consequences of alcohol consumption and various forms of problem drinking. Challenging conceptual and methodological issues confront researchers in testing hypotheses about the effects of alcohol problems on earnings, labor supply decisions, and the interactions of past alcohol problems, past decisions affecting labor market outcomes, and current labor market behavior. Studies that have examined the relationship between alcohol consumption and earnings have found that both heavy drinkers and individuals who abstain from alcohol completely have lower earnings than do individuals who drink at more moderate levels. However, studies have generally found pronounced negative effects of alcohol abuse and dependence on earnings and income levels. Research into the relationships between alcohol problems and individuals' decisions of whether and how much to work has yielded mixed results, with some findings varying especially by gender and age group. Finally, a relatively new area of research is finding support for hypotheses that alcohol problems may have indirect effects on earnings and employment by way of effects on educational achievement and marital status.

The past few years have seen enormous progress made, both conceptually and empirically, in specifying and estimating important policy-relevant economic relationships. Recent methodological advances (e.g., theories of advertising behavior and improved econometric techniques) have permitted and will continue to permit more ambitious empirical efforts in these areas of inquiry. When the availability of improved data sources that permit far more detailed investigations of these issues than have been possible to date is considered, one is left with considerable optimism about the prospects for meaningful economic analysis of behaviors associated with the use and abuse of alcohol, and for greater applicability of the findings of this research to policies that can reduce the adverse consequences of alcohol abuse. Research continues to illuminate the role that economic factors play in determining alcohol consumption as well as the incidence of various problems often associated with drinking. A growing body of research has established that consumption of beer, wine, and distilled spirits declines in response to increases in the prices or taxes for these beverages. However, drinkers with very high consumption levels may be much less sensitive than are moderate drinkers to price changes. Price and tax increases for alcoholic beverages are also associated with reductions in motor vehicle fatalities and other adverse outcomes frequently associated with alcohol consumption. Studies on alcohol and advertising continue to produce inconsistent results.

Chapter 9: Prevention of Alcohol Problems

The prevalence and impact of social and health-related problems associated with alcohol use underscore the need for effective approaches to prevent these problems. Research in prevention begins with foundational studies from biomedical and psychosocial perspectives and concludes with the actual testing of a single prevention strategy or multiple strategies in target populations. Additional steps in the research process include defining target populations at risk and factors associated with increased risk, identifying appropriate intervention objectives, developing viable intervention approaches, and determining the effectiveness of such approaches. Because alcohol problems are the consequence of complex interactions between individual perceptions and reactions to alcohol and the setting in which alcohol is consumed, prevention approaches may target the individual, the environment, or both.

Individual-level prevention programs deal with individuals and their proximal environments. Although by definition these programs target individuals, they often are delivered in group settings, such as the classroom, the family, or the workplace. Individual efforts have multiple goals, including changing beliefs or attitudes about alcohol, strengthening individual competencies, or restructuring environments to reduce the risk for alcohol-related problems.

Many individual-level approaches are school based because schools offer ready access to a target audience of current and potential young drinkers. School-based prevention programs are aimed at decreasing the prevalence and level of drinking among youth with the hope of preventing alcohol abuse later in life. In recent years, programs have been designed and implemented with greater scientific rigor and improved methodologies; these programs have provided promising results. For example, the Alcohol Misuse Prevention Study (AMPS), a resistance education program specifically designed for alcohol prevention, proved to be an effective intervention for alcohol misuse among high-risk sixth grade students. The positive effects of AMPS, which persisted in the students examined through grade 12, were produced partly by reducing adolescents' vulnerability to peer pressure.

Altering the normative beliefs of adolescents appears to be an important focus for school-based prevention approaches. Recently, evaluations of normative education efforts have demonstrated their usefulness in reducing alcohol use by participating students. Students exposed to a normative education curriculum within the Adolescent Prevention Trial had significantly lower alcohol use than those exposed to other curricula in the program. The Midwestern Prevention Project, which provided additional evidence for normative education effectiveness, yielded some declines in weekly prevalence rates of alcohol use among participating students, mostly by changing perceived peer-group norms about alcohol use.

Environmental-level prevention efforts consider the physical and social milieus that regulate exposure to alcohol or mediate the risk that drinking poses to an individual. Such approaches include warning efforts, community-based prevention programs, approaches that seek to limit alcohol availability or drinking and driving, and violence prevention. These broadly targeted approaches are critical to prevention in view of the ubiquity of alcohol use in the population, the difficulty in identifying all individuals at risk for alcohol problems, and the alcohol-induced impairment experienced at least occasionally by many drinkers. Research in this area has evaluated many aspects of the social and policy environment as applied to preventing alcohol problems, such as control of alcohol distribution, server intervention training, and minimum drinking age laws.

Interventions and public policies that affect alcohol availability may alter levels of alcohol consumption and alcohol-related problems. Studies have associated increased density of alcohol outlets with increased alcohol sales or higher percentages of drinkers. The privatization of alcohol distribution systems can yield changes in alcohol availability due to increased numbers of sales outlets, longer sale hours, and increased advertising and promotion. Studies evaluating the effects of privatization have shown that when States enact policy changes that eliminate alcohol retail monopolies and introduce licensed private sales outlets, sales and consumption of alcohol increase considerably. Information about relationships between changes in alcohol availability and changes in alcohol use can be useful for informing policy initiatives concerned with alcohol distribution.

Server training programs, which typically focus on educating bartenders, waiters, and waitresses about ways to avoid selling alcohol to minors and to people who are intoxicated, may provide an effective way to limit alcohol abuse and reduce injuries resulting from excessive drinking. Findings suggest that training can improve servers' knowledge of responsible alcohol service and intervention behavior toward patrons. In addition, implementation of a State-level compulsory training policy has been associated with significant reductions in single-vehicle nighttime traffic crashes. Further research is needed to determine the most effective types of server training.

Statistics demonstrate that drinking and driving is a significant public health concern—a substantial proportion of fatal and nonfatal traffic crashes in the United States is associated with alcohol use. Various strategies have been devised to address this problem, including lower allowable blood alcohol concentrations (BACs) for young drivers and designated driver programs. One strategy has involved providing taxi services during the winter holiday season for persons who appeared visibly intoxicated. Evaluation of this program found that it effectively deterred impaired drinkers from driving. A study of the use of designated drivers among fraternity members found that even when members agreed to designate a driver, they frequently forgot to do so. Even when they remembered, the designated driver typically drank, though at lower levels than usual. Thus, despite participants' favorable attitudes toward the concept of designating a driver, practical problems may limit application of this concept.

Prevention research has clearly shown that the establishment of 21 as the legal drinking age effectively reduces drinking and related problems, such as traffic crashes, unintentional injuries, and suicide among youth. Despite these reductions, most youth still drink. This has prompted studies to determine how these young people obtain alcohol. Drinking-age laws often are poorly enforced against persons who provide alcohol to underage youth, and recent investigations have shown that underage youth frequently purchase alcohol in various settings without being asked to provide identification to verify age.

Another approach to reducing rates of alcohol-related crashes has been to establish lower allowable BACs among young drivers. Allowable BACs for youth, determined by States, range from 0.00 to 0.05 percent. A recent study of States that implemented lower legal BACs for young drivers revealed a substantial drop in the proportion of fatal single-vehicle nighttime crashes and found that the lower the allowable BAC, the more profound the effect.

With the advent of research showing that prevention programs can be more effective when they target the individual as well as the social and environmental forces that encourage abusive drinking, programs that use multilevel communitywide efforts have become more common. Individual-level efforts in community programs work synergistically with environmental approaches to reduce or prevent alcohol problems in target populations. For example, an ongoing community program directed at sixth-, seventh-, and eighth-graders that includes school-based skill training curricula combined with peer leader, parent, and community support components successfully reduced alcohol use and the combination of cigarette and alcohol use among program participants.

Environmental approaches also are important components of communitywide prevention programs. Social, political, and economic factors that collectively may promote problem drinking are key considerations in the development of these communitywide programs. One such program emphasizes changing public policies, institutional structures, and organizational practices to reduce youth accessibility to alcohol; as yet, data on the effectiveness of this approach are not available. Other communitywide projects have effectively increased awareness, public support for alcohol prevention, and related attitudes. However, for many of these projects, changes in drinking behavior or in the prevalence of alcohol-related problems appear to be temporary.

Chapter 10: Treatment of Alcoholism and Related Problems

Although an increasing amount of evidence indicates that many people with alcohol problems can successfully stop or reduce their alcohol use without the help of formal treatment, those individuals with more severe alcohol dependence or with serious psychiatric or other drug use disorders are likely to participate in specialized alcoholism treatment programs as part of their recovery efforts. The development of successful treatment approaches for alcohol abuse or alcohol dependence requires rigorous tools for diagnosing alcohol dependence, screening patients who may be at risk for developing alcoholism, assessing patient characteristics toward the selection of treatment approaches, and determining effectiveness of treatment.

Recently, the American Psychiatric Association published the fourth edition of the *Diagnostic and*

Statistical Manual of Mental Disorders (DSM-IV), a widely used tool for diagnosing alcohol use disorders. The DSM-IV includes substantive changes in the diagnostic criteria for alcohol dependence and alcohol abuse, including a decrease in the number of symptoms that define alcohol dependence, an increase in the number of symptoms that define alcohol abuse, the addition of a temporal requirement that at least three dependence symptoms co-occur during a 12-month period, the inclusion of criteria for subtyping alcohol dependence on the basis of the presence or absence of the physiologic symptoms of withdrawal and tolerance, and the addition of descriptors that assist in characterizing recovery status of dependent patients. Research on the impact of these changes and comparison of the DSM-IV with other commonly used diagnostic systems will provide practical information to guide clinicians and researchers.

Formal diagnosis of alcohol use disorders includes patient assessment, which involves the use of structured interviews to determine patient characteristics that may affect treatment choice and treatment prognosis. Among behaviors thought to be important predictors of treatment success or failure are drinking-related beliefs such as self-efficacy (patient self-confidence in the ability to modify behavior), patient readiness to change, and drinking decisions based on alcohol-related expectancies. Assessment instruments continue to be developed to measure such behaviors and to help identify goals of treatment and determinants of treatment outcome.

Social behavior and functioning are thought to be closely associated with the outcome of alcoholism treatment. Accordingly, increased attention has been given to the definition and measurement of social support as it relates to the treatment of alcoholism. Most research has confirmed the importance of family and social support and of interventions focused on relationship enhancement in the recovery process.

For people who abuse but are not dependent on alcohol, a treatment approach known as brief intervention is a focus of current research. Brief intervention involves the early detection of harmful substance use before any physical dependence has developed. Typically, the approach employs a limited number of sessions to convey information about health risks associated with alcohol misuse, recommend behavioral change, and provide guidance for limiting alcohol use. The goal may be moderate drinking rather than total abstinence. Studies show that brief interventions can be quite effective. However, more research is needed to identify the types of patients best suited for this treatment.

Progress has continued in the development of pharmacologic agents for alcoholism treatment. Pharmacologic agents within various classes of drugs are being tested for alcoholism treatment, including detoxification agents to manage alcohol withdrawal, alcohol-sensitizing agents to deter patients from alcohol consumption during treatment, and anticraving agents to reduce the hunger for alcohol and the risk for relapse to drinking. The approval of the anticraving agent naltrexone for treatment of alcoholism by the Food and Drug Administration in 1994 represents an endorsement of this drug's effectiveness in reducing craving and preventing relapse to heavy drinking. Pharmacologic treatments also are useful for treating individuals who are alcohol dependent and have other psychiatric disorders, such as antisocial personality disorder. For example, nortriptyline appears to help alcohol-dependent patients with this disorder to maintain abstinence, apparently by reducing impulsive behaviors related to drinking.

Interventions to prevent relapse to drinking are an important component of alcoholism treatment. Expectancies about the effects of alcohol are believed to be important in peoples' decisions to begin and maintain drinking. Such expectancies are believed to be central to relapse occasions after treatment. Studies suggest that drinking decisions after treatment are influenced by both positive and negative alcohol expectancies and that both should be actively addressed during treatment interventions.

The appropriateness of controlled drinking as a therapeutic goal for alcoholism treatment remains highly controversial in the United States. Various patient characteristics influence whether controlled drinking is appropriate, including severity of dependence, extent of drinking history, psychological dependence, prior treatment episodes, and current liver damage. Treatment outcome studies have demonstrated successful maintenance of controlled drinking by a small subset of treated patients. According to one study, high initial levels of alcohol dependence and a positive family history of alcoholism were poor prognostic indicators for long-term asymptomatic drinking. However, patients who rejected the label of alcoholic and the goal of abstinence at treatment intake were most likely to be successful in achieving stable asymptomatic drinking through extended followup, suggesting the importance of attending to patients' self-assessment and treatment goals.

Chapter 11: Alcohol Health Services Research

Alcohol research has made significant advances in treating and preventing alcohol abuse and alcoholism, as determined largely through studies conducted in controlled experimental settings. Alcohol health services research examines the effectiveness of these interventions in real-world settings and characterizes factors related to organization, management, and financing that facilitate the implementation or availability of interventions. The ultimate goal of this relatively new and evolving area of investigation is to improve the accessibility, quality, effectiveness, and cost-effectiveness of prevention and treatment for alcohol abuse and alcoholism.

Currently, alcohol health services research is taking place within a context of dramatic change in the organization and financing of health care. Although health care services have long been subject to changes in policy and practice, current transformations are more profound and fundamental than any before. This state of flux makes research theoretically and methodologically difficult. Most published research in alcohol health services has been based on work conducted before changes in the health care system and provides baseline data that will help investigators characterize the impact of change and assess new intervention approaches.

Many recent studies have concentrated on determining the availability of alcohol treatment services generally and to different population groups. One investigative approach has been to examine changes in treatment units over time. For example, based on data from the National Drug and Alcoholism Treatment Utilization Survey, the number of alcohol only and alcohol and other drug treatment units increased by nearly 150 percent between 1982 and 1993. From 1982 to 1992, the percentage of programs offering specialized services for women also increased. In addition, due to set-asides mandated through Federal legislation, publicly funded alcohol treatment programs now serve a variety of populations with special treatment needs, including women, children and adolescents, injection drug users, and persons referred from courts for alcohol-related offenses such as drinking and driving.

Availability of alcohol treatment and prevention services is closely tied to accessibility and use of such services. Among factors shown to influence entry into treatment are gender, age, marital status, and ethnicity. Studies have shown that for women, factors predicting entry into treatment include being older, unmarried, and white and having a lower level of education, employment, and income; for men, the corresponding factors include having experienced alcohol-related social consequences as well as being older and a member of an ethnic minority. Access to alcohol health services may not be equal across ethnic groups. For example, national data show that the percentage of Hispanics in public alcohol treatment programs is lower than their problem drinking rates, while the percentage of African Americans in such programs was higher than their problem drinking rates. One study has shown that the use of treatment services is influenced by ethnic differences in health beliefs that motivate individuals to seek treatment.

Increasingly, managed care programs are limiting costs by restricting unnecessary treatment. Initially, managed care arrangements affected only private treatment; recently, State and county systems as well as public insurance have begun to adopt similar approaches for the sake of improved economic efficiency. In addition, managed care organizations have made a pronounced effort to decrease the use of inpatient services because of their greater expense relative to outpatient services. Unfortunately, few controls are used to ensure that cost-containment efforts do not impede accessibility to treatment or affect the quality of treatment.

Cost and cost-effectiveness are fundamental issues in alcohol health services research; the key question concerns which treatment approaches are most effective for the least cost. However, only a few studies have directly addressed the cost-effectiveness of alcohol treatment services. Recent studies have analyzed data on the overall cost-effectiveness of alcohol treatment and data from field experiments of inpatient versus outpatient treatment; findings may help address issues of cost and outcome as applied to future cost-effectiveness and cost offset (cost savings). One study, a meta-analysis of numerous treatment modalities, suggested that brief motivational counseling was the most cost-effective and that aversion therapy was among the least cost-effective treatment approaches. Other analyses have shown cost-offset benefits to alcohol treatment for people in residential treatment, and several investigations have shown that outpatient treatment is at least as effective as inpatient treatment. This area of alcohol health services research merits further development. In addition, research on matching treatment to need, on treatment effectiveness, and on evaluating different organizational systems for structuring treatment will help guide the development of future services and establish priorities for insurance coverage.

Conclusion

The *Ninth Special Report to the U.S. Congress on Alcohol and Health* summarizes the current state of alcohol research and presents the progress that has been made in unraveling the mysteries of alcohol abuse and alcoholism since the publication of the *Eighth Special Report.* These research advances lay the foundation for future studies probing the causes, treatment, and prevention of alcohol use problems.

Chapter 1

Epidemiology of Alcohol Use and Alcohol-Related Consequences

Introduction

Alcohol epidemiology describes and explains the distribution of alcohol use, abuse, and dependence and the associated health and social consequences. Surveillance data are gathered from alcohol sales information, U.S. vital statistics, and hospital records to track alcohol consumption and its related problems. Population-based survey research examines the context, volume, and specific drinking patterns that lead to particular alcohol-related problems. Information reported in this chapter is largely descriptive. Knowledge gained from alcohol epidemiology provides a foundation for monitoring the health of our population, developing and evaluating prevention and treatment services for alcohol problems, and establishing alcohol-related social policies. Further, these data raise compelling questions that can serve as the basis for subsequent research exploring mechanisms that may explain the data observations.

Increased availability of information from multiple sources, including international statistics, makes alcohol epidemiology particularly relevant at this time because these data allow for greater precision in assessing alcohol use and more thorough analyses of the prevalence of alcohol problems and related consequences at the aggregate level. This ability is important because new knowledge about shifts in consumption and problem rates within subgroups can have critical implications for programs and policies.

This chapter provides a review of quantitative studies on alcohol use and alcohol-related problems in the U.S. population. The review is supplemented with comparative international data where available. General topics include definitions of alcohol consumption, alcohol-related consequences, and alcohol abuse and dependence. The chapter also includes descriptive information on special population groups (i.e., women, youth, older adults, and ethnic minorities). The final section summarizes findings reported in the review.

Defining Alcohol Abuse and Alcoholism

Critical to epidemiologic research and to subsequent intervention and treatment are accepted definitions or classifications of the diseases or conditions under investigation. In recent years, an evolution of definitions, concepts, and diagnostic criteria for alcohol use problems has played an integral role in epidemiologic research.

Two major systems for diagnosing alcohol abuse and dependence are available to clinicians and researchers: the international diagnostic system published by the World Health Organization (WHO) in 1992, *International Classification of Diseases, Tenth Revision: Clinical Descriptions and Diagnostic Guidelines* (ICD-10), and the U.S. system established by the American Psychiatric Association (APA), the 1994 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). Both classification systems are based on the concept of an alcohol dependence syndrome, in which a cluster of recognizable symptoms (e.g., impaired control over intake, withdrawal from alcohol, tolerance, and drinking despite problems) occurs in the alcohol-dependent patient (APA 1994; Edwards and Gross 1976; WHO 1992). According to DSM-IV, alcohol dependence is a cluster of cognitive, behavioral, and physiologic symptoms which indicate that a person continues to drink despite significant alcohol-related problems. Alcohol abuse generally is characterized as repetitive patterns of drinking in harmful situations with adverse consequences, including impaired ability to fulfill responsibilities or negative effects on social/interpersonal functioning and health.[1] The term "alcohol-related consequences" refers not to a specific diagnostic category but to a wide range of alcohol-related problems that includes difficulties with family members and friends, work problems, legal troubles, accidents and casualties, and health consequences. It is important to note that alcohol-related problems do not necessarily involve heavy drinking patterns.

> *According to DSM-IV, alcohol dependence is a cluster of cognitive, behavioral, and physiologic symptoms which indicate that a person continues to drink despite significant alcohol-related problems.*

Research-based increases in knowledge about alcohol abuse and alcohol dependence have led to continued development and refinement of DSM diagnostic criteria over the past 16 years. DSM-III criteria, established in the third edition of the diagnostic manual (APA 1980), required a pattern of alcohol use and related impairment of social or occupational functioning to establish a diagnosis of alcohol abuse; a diagnosis of alcohol dependence required the presence of tolerance or symptoms of withdrawal in addition to evidence of either loss of control or social or physical problems due to alcoholism. In 1987, the criteria for alcohol abuse and dependence were revised in DSM-III-R (APA 1987). The revision incorporated a broadened concept of dependence, diminishing the relative importance of tolerance and withdrawal and increasing the emphasis on the "salience"[2] of substance use. A diagnosis of alcohol abuse, considered to be indicative of an ongoing but subthreshold alcohol problem, required continued use of alcohol despite social, occupational, psychological, or physical problems in addition to recurrent alcohol use in physically hazardous situations.

Revisions to DSM-III-R, initially released in 1991 and referred to as "proposed DSM-IV criteria," were developed in response to criticism that two abuse criteria in DSM-III-R overlapped with dependence and thus broadened the definition of dependence while correspondingly narrowing the definition of abuse (APA 1991). In 1994, the APA published the final DSM-IV criteria, which provide a greater distinction between alcohol abuse and dependence and return physiologic indicators to the definition of dependence (APA 1994). The DSM-IV criteria reduce the number of symptoms that define alcohol dependence (from nine in DSM-III-R to seven in DSM-IV), increase the number of symptoms that define alcohol abuse (from two in DSM-III-R to four in DSM-IV), and add a temporal requirement that at least three dependence symptoms co-occur during a 12-month period as well as criteria for subtyping alcohol dependence on the basis of the presence or absence of the physiologic symptoms of withdrawal and tolerance.

Variations in DSM criteria can influence the outcome of epidemiologic research, potentially leading to marked differences in prevalence estimates of alcohol abuse and dependence. Some studies discussed in this chapter present results based on a single set of criteria, others compare rates using DSM-III-R and DSM-IV sets of criteria, and still others include comparisons with ICD-10 criteria.

Alcohol Consumption: Trends and Patterns

Per Capita Consumption

How much and what types of alcoholic beverages (beer, wine, and spirits) Americans drink and whether overall drinking levels are increasing or decreasing can be determined by monitoring the sales of alcoholic beverages (Brooks et al. 1989). Per capita consumption, derived primarily from sales data, represents an estimate of the average amount of alcohol used per individual. Through the Alcohol Epidemiologic Data System of the National Institute on Alcohol Abuse and Alcoholism, sales data are obtained (where available) from every State and the District of Columbia. For States that do not provide sales data, shipment data from main beverage industry sources are used. "Apparent per capita consumption" is calculated by dividing alcoholic sales data (or shipment data) from every State and the District of Columbia by the U.S. population aged 14 years or older (Williams et al. 1994). Thus, the estimates attribute average consumption to all people in this population, regardless of their actual consumption. Apparent per capita consumption is expressed in gallons of pure alcohol; it is calculated by multiplying total gallons of each beverage type by a conversion factor that represents the average alcohol content of each beverage type (0.045 for beer, 0.129 for wine, and 0.414 for spirits) and then summing over all three beverages (Williams et al. 1994).

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[1] The ICD-10 uses the category harmful use, rather than alcohol abuse, which emphasizes consequences that may be either physical or psychological in nature. These alcohol-related consequences are somewhat different from those emphasized by the DSM-IV.

[2] Salience refers to a state in which a person places a higher priority on continued drinking than on other important life activities, has strong subjective urges to drink, and develops an increasingly rigid pattern of regular drinking.

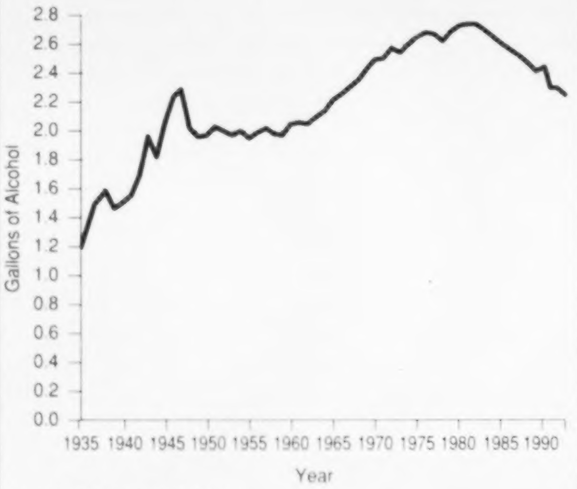
Estimates of apparent per capita consumption have several limitations. First, because the data are derived from sold or shipments of alcohol, per capita statistics do not include home production, illegal production, stockpiling, breakage, or untaxed alcohol brought into the country by tourists; however, duty-free purchases of alcohol made by Americans returning from abroad are included. Second, researchers using these data assume that alcohol will be consumed during the year in which it was purchased. Thus, increases in per capita consumption (based on sales data) in any given year also may reflect an increase in purchases made in anticipation of higher taxes to be imposed on alcoholic beverages during the following year.

In the years just preceding World War II, alcohol use increased rapidly then stabilized between about 1947 and 1961 (figure 1a). Consumption steadily increased from the early 1960s and reached a peak in 1980 and 1981, after which it began to decline (Williams et al. 1995).

The decline continued between 1990 and 1991, when overall per capita alcohol consumption dropped 6.1 percent, from 2.46 to 2.31 gallons of pure alcohol (Williams et al. 1995). Overall per capita consumption did not change between 1991 and 1992, but in 1993 it dropped 2.6 percent to 2.25 gallons of alcohol. The 1993 per capita consumption level represents the lowest level since 1964 (table 1).

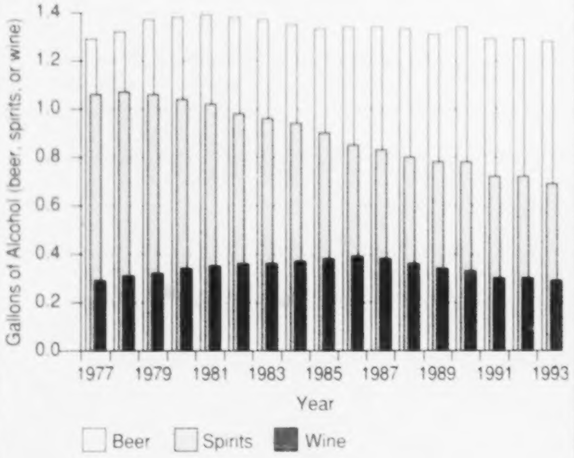
The overall decrease in alcohol use since 1982 is not uniform across beverage types (Williams et al. 1995). Consumption of beer, wine, and spirits has varied between 1977 and 1993 (figure 1b). Beer has made the greatest contribution to apparent per capita alcohol consumption in the United States and wine has made the least. Data on use for individual years demonstrate that beer consumption levels decreased from 1981 to 1985, fluctuated somewhat through 1992, and ended in 1993 1 percent lower than in 1977. For wine, per capita consumption generally increased each year through 1986 and then decreased from 1987 through 1991. Per capita

Figure 1a. Total per capita alcohol consumption, United States, 1935–1993.



Source: Williams et al. 1995.

Figure 1b. Per capita alcohol consumption by beverage type, United States, 1977–1993.



Source: Williams et al. 1995.

Table 1. Apparent per capita alcohol consumption, United States, 1850–1993.* Gallons of alcohol, based on population aged 15 years and older before 1970 and on population aged 14 years and older thereafter.

Year	Beer	Wine	Spirits	All Beverages	Year	Beer	Wine	Spirits	All Beverages
1993	1.28	0.29	0.69	2.25	1957	0.97	0.22	0.80	1.99
1992	1.29	0.30	0.72	2.31	1956	1.00	0.22	0.81	2.03
1991	1.29	0.30	0.72	2.31	1955	1.01	0.22	0.77	2.00
1990	1.34	0.33	0.78	2.46	1954	1.01	0.21	0.74	1.96
1989	1.31	0.34	0.78	2.43	1953	1.04	0.20	0.77	2.01
1988	1.33	0.36	0.80	2.49	1952	1.04	0.21	0.73	1.98
1987	1.34	0.38	0.83	2.54	1951	1.03	0.20	0.78	2.01
1986	1.34	0.39	0.85	2.58	1950	1.04	0.23	0.77	2.04
1985	1.33	0.38	0.90	2.62	1949	1.06	0.22	0.70	1.98
1984	1.35	0.37	0.94	2.65	1948	1.07	0.20	0.70	1.97
1983	1.37	0.36	0.96	2.69	1947	1.11	0.16	0.76	2.03
1982	1.38	0.36	0.98	2.72	1946	1.07	0.24	0.99	2.30
1981	1.39	0.35	1.02	2.76	1945	1.17	0.20	0.88	2.25
1980	1.38	0.34	1.04	2.76	1944	1.13	0.18	0.76	2.07
1979	1.37	0.32	1.06	2.75	1943	1.00	0.17	0.66	1.83
1978	1.32	0.31	1.07	2.71	1942	0.90	0.22	0.85	1.97
1977	1.29	0.29	1.06	2.64	1941	0.81	0.18	0.71	1.70
1976	1.27	0.32	1.10	2.69	1940	0.73	0.16	0.67	1.56
1975	1.26	0.32	1.11	2.70	1939	0.75	0.14	0.62	1.51
1974	1.25	0.31	1.11	2.67	1938	0.75	0.13	0.59	1.47
1973	1.20	0.31	1.10	2.62	1937	0.82	0.13	0.64	1.59
1972	1.17	0.30	1.09	2.56	1936	0.79	0.12	0.59	1.50
1971	1.15	0.31	1.12	2.59	1935	0.68	0.09	0.43	1.20
1970	1.14	0.27	1.11	2.52	1934	0.61	0.07	0.29	0.97
1969	1.12	0.26	1.13	2.51	(Prohibition)				
1968	1.09	0.26	1.10	2.45	1916–1919	1.08	0.12	0.76	1.96
1967	1.07	0.25	1.05	2.37	1911–1915	1.48	0.14	0.94	2.56
1966	1.06	0.24	1.02	2.32	1906–1910	1.47	0.17	0.96	2.60
1965	1.04	0.24	0.99	2.27	1901–1905	1.31	0.13	0.95	2.39
1964	1.04	0.24	0.95	2.23	1896–1900	1.19	0.10	0.77	2.06
1963	1.01	0.23	0.91	2.15	1891–1895	1.17	0.11	0.95	2.23
1962	0.99	0.22	0.90	2.11	1881–1890	0.90	0.14	0.95	1.99
1961	0.97	0.23	0.86	2.06	1871–1880	0.56	0.14	1.02	1.72
1960	0.99	0.22	0.86	2.07	1870	0.44	0.10	1.53	2.07
1959	1.00	0.22	0.84	2.06	1860	0.27	0.10	2.16	2.53
1958	0.96	0.22	0.80	1.98	1850	0.14	0.08	1.88	2.10

*Sources: Williams et al. 1993. Data updated from Hyman et al. 1980.

consumption of wine in 1993 was the same as it was in 1977. Almost all of the recent decrease in alcohol use, however, can be attributed to a decline in the use of spirits. Per capita consumption of spirits in 1993 was 34.9 percent below the 1977 level.

Trends in alcohol use also differ by State (figure 2) and by region of the country (figures 3a–3d). Between 1977 and 1993, overall per capita consumption among the 50 States and the District of Columbia declined, on average, by 14.8 percent. Mississippi and Arkansas showed increases or no change in levels of consumption, but 11 States and the District of Columbia had a 20-percent or greater decrease (Williams et al. 1995).

Data on regional total per capita consumption from 1977 to 1993 indicate that overall per capita consumption throughout the period was highest in the West; consumption levels in the other three regions have been similar since 1990 (see figure 3a). Per capita consumption by region for each beverage type is presented in figures 3b–d. A dramatic decline in consumption of spirits for all regions began in both the West and the South a few years before 1981. All regions showed a more modest decline in both beer and wine use between 1981 and 1993 (Williams et al. 1995).

Several factors may have influenced the decrease in apparent alcohol consumption, including less tolerant national attitudes toward drinking, increased societal and legal pressures and actions against drinking and driving, and increased health concerns of Americans. The apparent increase in consumption within all regions in 1990 may have resulted from anticipation of increased Federal taxes on beverage alcohol enacted in January 1991.

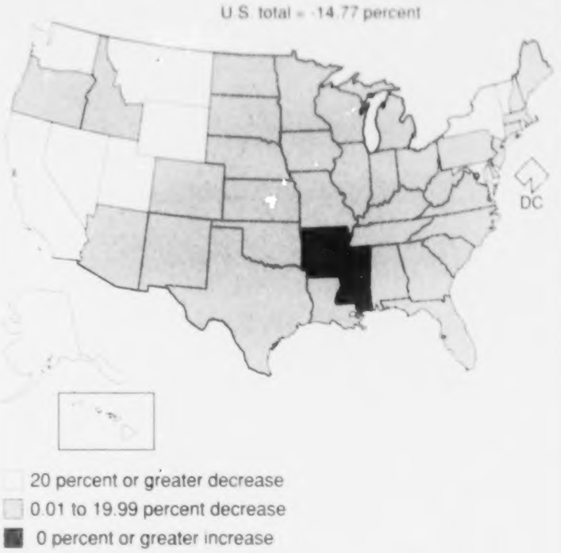
Table 2 presents data on international trends in per capita consumption in 1970, 1980, and 1990 for 23 countries within the Organization for Economic Cooperation and Development (Edwards et al. 1994). Over this 20-year period, alcohol use declined in France, Italy, and Sweden. In 15 other countries, alcohol use increased from 1970 to 1980 but declined from 1980 to 1990. Only five countries—Denmark, Finland, Great Britain, Japan, and Luxembourg—had overall increases in alcohol use during this 20-year period; however, it is notable that consumption in these countries initially (i.e., in 1970) was very low compared with consumption in the other countries studied.

Although investigations of per capita alcohol consumption provide a wealth of useful knowledge, they do not reveal demographic correlates and patterns of alcohol use. Individual-level data collected from national alcohol surveys provide a better description of alcohol use and drinking patterns in the United States.

Drinking Patterns

To understand shifts in alcohol use in the general population and in specific subgroups within the population, researchers assess drinking patterns by using survey data. National alcohol surveys are, for the most

Figure 2. Percent change in total per capita alcohol consumption by State, United States, 1977–1993.


U.S. total = -14.77 percent
DC
20 percent or greater decrease
0.01 to 19.99 percent decrease
0 percent or greater increase

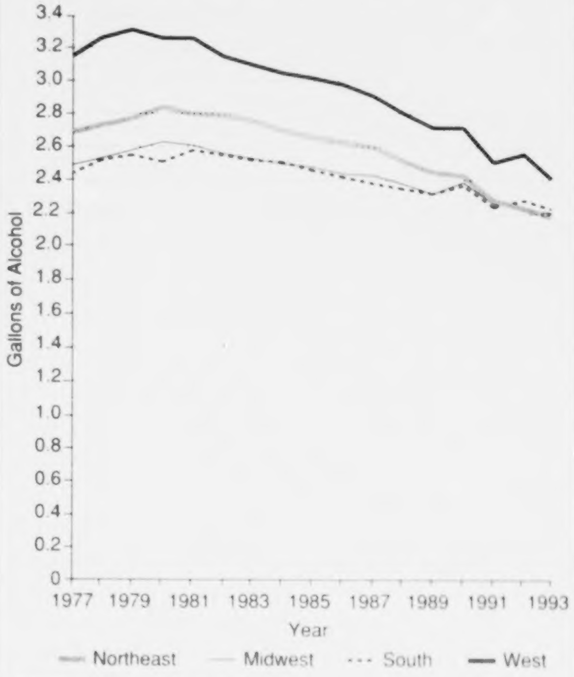
Source: Williams et al. 1995.

Table 2. Per capita alcohol consumption (litres of ethanol) in Organization for Economic Cooperation and Development countries, 1970–1990.

	1970	**1980**	**1990**
Australia	8.1	9.6	8.4
Austria	10.5	11.0	10.4
Belgium	8.9	10.8	9.9
Canada	6.1	8.6	7.5
Denmark	6.8	9.1	9.9
Finland	4.4	6.4	7.7
France	16.2	14.9	12.7
Germany	10.3	11.4	10.6
Great Britain	5.3	7.3	7.6
Iceland	3.2	3.9	3.9
Ireland	5.9	7.3	7.2
Italy	13.7	13.0	8.7
Japan	4.6	5.4	6.5
Luxembourg	10.0	10.9	12.2
Netherlands	5.6	8.8	8.2
New Zealand	7.6	9.6	7.8
Norway	3.6	4.6	4.1
Portugal	9.9	11.0	9.8
Spain	11.6	13.6	10.8
Sweden	5.8	5.7	5.5
Switzerland	10.7	10.8	10.8
Turkey	0.5	0.7	0.6
United States of America	6.7	8.2	7.5

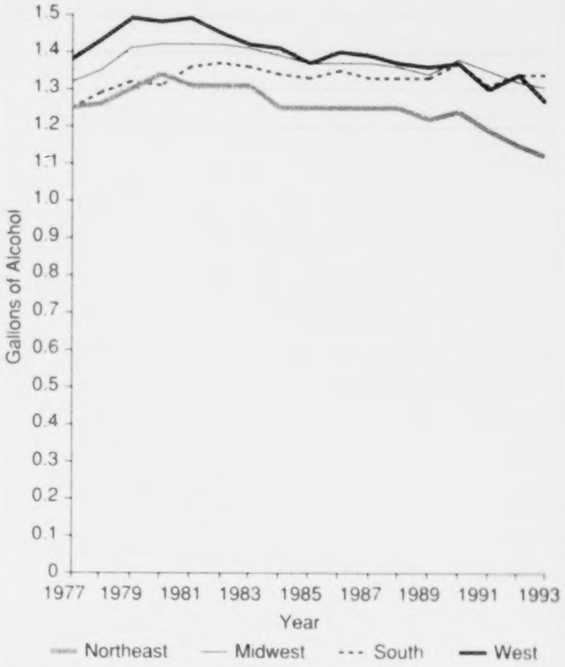
Source: Edwards et al. 1994. Reprinted from *Alcohol Policy and the Public Good* 1994 by permission of Oxford University Press.

Figure 3a. Total per capita alcohol consumption by region, United States, 1977–1993.



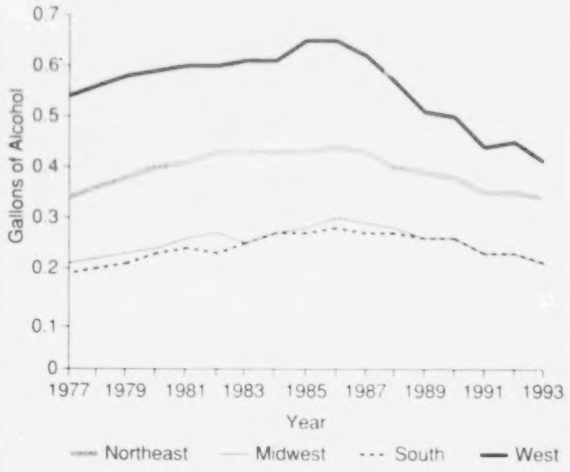
Source: Williams et al. 1995

Figure 3b. Per capita alcohol consumption from beer by region, United States, 1977–1993.



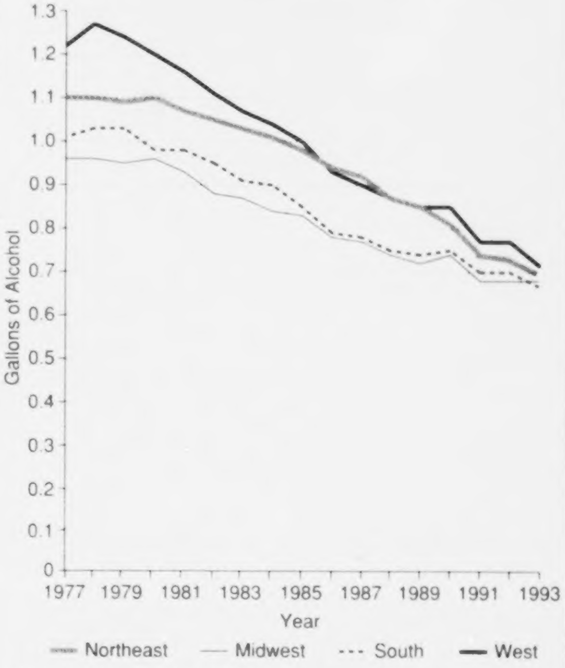
Source: Williams et al. 1995

Figure 3c. Per capita alcohol consumption from wine by region, United States, 1977–1993.



Source: Williams et al. 1995

Figure 3d. Per capita alcohol consumption from spirits by region, United States, 1977–1993.



Source: Williams et al. 1995

part, based on household populations and exclude institutionalized and homeless persons. The primary studies used to assess overall drinking patterns and trends in the United States include the large-scale 1983 and 1988 National Health Interview Surveys (NHISs) and the smaller 1984 and 1990 National Alcohol Surveys (NASs). Drinking patterns and trends in specific subgroups of the population (e.g., women, adolescents, and ethnic minorities) have also been assessed using these and other data.

At a minimum, most surveys collect frequency-quantity data, which involves asking survey participants how often they consume alcohol and how many drinks they usually have during a specified period of time. Collected data then are used to categorize respondents according to the amount of alcohol consumed. Often, participants are also asked about social and medical influences and consequences of alcohol use. For example, they may be asked how peer pressure affects their alcohol intake, how their level of intake affects family and work relationships, or how alcohol consumption affects their health.

The validity of self-reported data on alcohol consumption and alcohol-related problems is an important issue in analyzing these data. On an aggregate level, self-reported alcohol use derived from national surveys has accounted for only 40 to 60 percent of the alcohol sold in this country (Midanik 1982). However, most national surveys involve samples derived from households; therefore, the heaviest alcohol users (e.g., homeless persons and those residing in institutions) are typically not included. On an individual level, some data have suggested that heavy users of alcohol and drinkers with problems tend to underestimate intake (Midanik 1988). Although there is no standard against which individual-level self-reported data can be compared, assessments of methodologic studies indicate that for the general population, self-reports of alcohol use are fairly accurate. Furthermore, extensive training and monitoring of interviewers, careful wording of interview items to avoid ambiguity, interviewing respondents in a private setting, and assuring the respondent that information provided is confidential enhance the accuracy of self-reported data (Clark 1991).

Midanik and Clark (1994) analyzed data from the 1984 and 1990 NASs to determine whether certain shifts in alcohol use are continuing and to identify population subgroups experiencing such shifts. The investigators reported a significant decrease in the proportion of current drinkers of any alcoholic beverage (69.6 percent in 1984 versus 65.0 percent in 1990). Beverage-specific current consumption for wine, beer, and spirits also declined over this period. With respect to weekly and heavier drinking, significant reductions were also observed: Weekly drinking dropped from 35.9 percent in 1984 to 29.0 percent in 1990, and heavier drinking (defined as five drinks on one occasion at least weekly) decreased from 6.2 percent to 3.9 percent over this 6-year period. These findings remained significant when demographic characteristics of the population were controlled in statistical analyses.

Using NAS data, Midanik and Clark (1994) also examined whether the changes in drinking patterns were uniform across demographic subgroups. Drinking patterns within 11 demographic groups are presented in table 3. The investigators observed a similar downward trend in alcohol consumption over the 6-year study period for all the consumption measures and most of the selected population subgroups. Many of the reductions were not statistically significant, in part because of the small sample sizes within subgroups. However, the decrease in current drinkers was significant for men 30 to 39 years old and women 60 years and older, persons who had never married, whites, persons with household incomes below the median, respondents who work full time, certain Protestant religious groups (defined in the third footnote in table 3), college graduates, and persons who live in small metropolitan and nonmetropolitan areas. For weekly drinkers, the researchers reported a significant decrease for both men and women, respondents 18 to 39 years old, married persons, whites, persons with household incomes above the median, persons working full time or part time, the Protestant religious groups previously cited, respondents who felt religion was very or somewhat important, high school graduates, respondents from larger and smaller regions, and respondents from the Midwest and Pacific regions of the United States. Finally, significantly fewer heavier drinking episodes (five or more drinks on one occasion at least weekly) were reported by respondents who were male, between 30 and 39 years old, married, and white; had household incomes above the median; were working full time; were members of the previously cited Protestant religious groups; reported that religion was somewhat important; were high school graduates; were living in smaller metropolitan areas; and were from the Midwest.

Table 3. Demographic characteristics of drinkers, 1984 and 1990.

	1984	1990	Current Drinkers, %		Weekly Drinkers, %		Drinkers of Five or More Drinks,[*] %	
	(N = 5,221)	(N = 2,058)	1984	1990	1984	1990	1984	1990
Gender								
Male	2,093	869	75.9	71.2	48.9	40.0[†]	10.6	6.5[†]
Female	3,128	1,189	63.9	59.4	24.4	18.8[†]	2.2	1.4
Age, years								
18–29	1,515	442	77.8	73.1	40.1	32.2[†]	10.3	7.0
30–39	1,277	520	77.6	70.7	42.3	30.0[†]	7.7	3.0[†]
40–49	711	330	68.9	68.4	33.5	29.0	4.6	3.8
50–59	593	228	66.1	61.9	36.9	32.8	4.2	3.3
60+	1,092	538	53.5	49.4	25.5	22.4	1.2	1.5
Gender and Age								
Male								
18–29	621	201	81.7	76.5	52.3	44.4	17.6	11.0
30–39	511	209	86.7	72.5[†]	60.0	39.2[†]	12.4	4.3[†]
40–49	305	146	77.5	71.8	44.7	38.5	6.0	6.8
50–59	235	102	70.7	64.6	48.4	43.5	8.7	6.2
60+	413	211	58.8	65.6	36.0	34.8	2.5	3.1
Female								
18–29	894	241	73.9	69.7	28.2	19.7	3.1	3.0
30–39	766	311	69.3	69.0	26.4	20.9	3.5	1.7
40–49	406	184	62.3	65.1	24.8	20.1	3.6	1.0
50–59	358	126	62.2	59.8	26.9	24.2	0.2	0.9
60+	679	327	48.9	37.0[†]	16.5	12.9	0.2	0.2
Marital Status								
Married	2,619	1,191	68.5	65.7	35.0	28.1[†]	4.8	2.3[†]
Separated	367	84	74.8	69.2	38.4	19.9	4.3	0.8
Divorced	554	221	71.9	69.0	38.5	36.1	7.2	7.9
Widowed	578	220	51.5	41.6	22.3	17.0	2.3	1.9
Never married	1,101	341	78.8	69.6[†]	43.2	35.3	12.1	8.7
Ethnicity								
Black	1,947	261	61.6	61.6	29.5	25.8	4.1	3.5
White	1,777	1,570	71.0	65.9[†]	37.3	30.2[†]	6.4	3.5[†]
Hispanic	1,453	150	65.4	66.6	29.5	26.5	4.6	8.9
Other	44	77	64.1	57.0	31.0	21.6	11.1	1.4

[*] Persons who reported having five or more drinks on one occasion at least once a week during the previous year.

[†] $P < 0.05$.

[‡] Defined as Protestant (no denomination mentioned), Lutheran, Presbyterian, Episcopalian, Unitarian/Universalist, Quaker, or Congregational.

[§] Defined as Baptist, Methodist, fundamentalist Protestant, Pentecostal, Assembly of God, Church of God, Nazarene, Holiness, Apostolic, Evangelical, Sanctified, Christian Church/Disciples of Christ, United Church of Christ, Christian Reformed, Jehovah's Witness, Seventh Day Adventist, Mormon/Latter Day Saints, Brethren, Spiritualist, Rastafarian, and Salvation Army.

[‖] Northeast includes New England and Mid-Atlantic States; Midwest includes East North Central and West North Central States; Pacific includes only Pacific States; South includes South Atlantic, East South Central, and West South Central States; Mountain includes only Mountain States.

Note: Percentages are based on weighted sample sizes (effective N's of 1,228 for the 1984 survey and 1,150 for the 1990 survey). Subgroup N's may not equal total because of missing data.

Table 3. Demographic characteristics of drinkers, 1984 and 1990 *(continued)*.

	1984	1990	Current Drinkers, %		Weekly Drinkers, %		Drinkers of Five or More Drinks,* %	
	(N = 5,221)	(N = 2,058)	1984	1990	1984	1990	1984	1990
Household Income								
Above median	1,463	913	78.2	73.8	42.6	31.7†	5.8	2.5†
Below median	3,405	1,031	62.0	56.1†	30.0	25.5	6.7	4.9
Employment Status								
Work full time	2,456	1,040	78.8	73.7†	44.1	35.2†	8.4	4.3†
Work part time	452	241	72.6	65.6	34.6	18.9†	5.4	3.6
Retired	717	343	53.0	51.7	23.9	25.1	1.2	2.0
Homemaker	892	227	52.3	44.2	19.8	12.8	1.9	1.1
Other	702	207	66.2	59.9	34.5	30.4	8.5	7.3
Religion								
Catholic	1,730	510	82.5	78.6	43.0	37.3	8.5	6.7
Jewish	58	36	88.2	91.8	50.6	30.2	0.3	0.0
Liberal Protestant‡	412	360	83.4	72.6†	47.6	36.1†	5.4	1.0†
Conservative Protestant§	2,568	887	53.6	51.1	23.6	19.3	3.6	2.2
Other	437	197	79.3	75.4	48.8	37.1	13.4	9.3
Importance of Religion								
Very	3,406	1,087	56.5	51.5	23.8	18.8†	2.5	1.4
Somewhat	1,357	696	84.0	81.0	48.3	39.0†	9.7	5.4†
Not really	283	180	85.8	75.7	53.8	41.6	10.2	9.9
Not at all	112	89	81.9	77.6	54.4	47.1	15.3	9.0
Education								
< High school	2,063	479	53.6	50.4	27.8	23.5	5.2	6.3
High school	1,628	779	71.9	66.3	35.3	26.4†	9.2	3.8†
Some college	935	401	73.2	70.2	37.3	30.6	4.4	3.1
College graduate	583	397	84.0	75.4†	47.9	39.8	3.4	1.8
Urbanicity								
Metropolitan area > 50,000 population	2,796	889	72.5	67.3	39.7	31.2†	7.2	4.8
Metropolitan area ≤ 50,000 population	850	555	78.6	70.0†	39.6	30.6†	7.1	2.7†
Nonmetropolitan area	1,574	614	63.5	56.3†	31.6	23.7†	4.9	3.7
Region								
Northeast	990	346	80.1	75.5	41.1	37.6	3.4	3.9
Midwest	883	612	74.9	69.3	41.4	27.1†	7.6	3.3†
Pacific	815	266	74.6	64.8	41.7	28.0†	8.5	5.0
South	2,322	698	57.8	58.8	26.8	27.1	4.9	3.7
Mountain	211	136	62.1	53.7	31.5	23.2	12.2	4.2

Source: Midanik and Clark 1994. Reprinted by permission. Midanik, L.T., and Clark, W.B. Demographic distribution of US drinking patterns in 1990: Description and trends from 1984. *American Journal of Public Health* 84(8):1218–1222, 1994. Copyright 1994. American Public Health Association.

Table 4. Proportion of abstainers and frequency of consumption in countries of the European Community.

	Abstainers		Frequency* (Situations/week)			
	Males %	Females %	Males Mean	Males S.D.	Females Mean	Females S.D.
Denmark	2.1	6.1	4.7	3.1	3.1	2.3
West Germany	5.8	8.9	5.0	3.5	2.8	2.3
Netherlands	11.4	24.1	4.7	3.8	3.0	2.9
United Kingdom	13.7	23.5	4.1	3.2	2.5	2.3
Ireland	24.5	36.3	3.1	2.3	1.9	1.6
Belgium	9.7	17.4	5.5	4.3	3.7	3.3
Luxembourg	10.6	22.3	5.0	3.5	3.1	3.2
France	7.5	15.3	6.5	4.3	3.6	3.3
Italy	10.3	21.5	6.5	4.2	4.1	3.5
Greece	6.2	27.1	6.0	5.0	3.0	3.1
Spain	17.3	32.1	7.5	5.6	3.9	3.4
Portugal	10.7	32.6	7.1	4.4	3.7	2.7
European Community	10.8	22.3	5.5	4.2	3.2	2.9

*Abstainers excluded.

Source: Hupkens et al. 1993. Reprinted by permission. Hupkens, C.L.H.; Knibbe, R.A.; and Drop, M.J. Alcohol consumption in the European Community: Uniformity and diversity in drinking patterns. *Addiction* 88(10):1391–1404, 1993. Carfax Publishing Company, Oxford, U.K.

Age shifts in the American population cannot be overlooked when evaluating alcohol intake. In general, alcohol consumption is lowest at the extremes of the age distributions used to calculate apparent per capita consumption. Thus, increased percentages of both the older and the teenage populations could contribute to the overall decline in apparent alcohol consumption in the United States.

Global comparisons of drinking patterns are important in alcohol epidemiology. In recent research, Hupkens et al. (1993) analyzed data from the 1988 "Eurobarometer" survey that gathered information from respondents in 12 countries in an effort to describe and compare drinking patterns in the European Community (table 4). Approximately 10 percent of men and more than 20 percent of women abstained from alcohol. In all countries surveyed, women were at least twice as likely to be abstainers as men, but the proportion of abstainers varied substantially among countries. For example, Denmark and West Germany had the lowest proportion of abstainers, while Ireland, Portugal, and Spain had the highest proportion.

Among drinkers in the European Community, frequency of drinking also varied from country to country. The investigators noted that men and women from Southern countries included in the survey (Luxembourg, France, Italy, Greece, Spain, and Portugal) drank more frequently than those in the northern countries (Denmark, West Germany, the Netherlands, the United Kingdom, Ireland, and Belgium). Men drank approximately six times per week, and women drank three times per week.

Adverse Consequences of Drinking

Morbidity and Mortality

Data on alcohol-related morbidity and mortality are a useful resource for tracking health effects of alcohol consumption over time and for measuring the effect of prevention and treatment efforts. Three types of data, alcohol-related fatal traffic crashes, liver cirrhosis mortality, and alcohol-related morbidity, are presented in this chapter; all are derived from surveillance reports prepared by the Alcohol Epidemiologic Data System.

Alcohol-Related Fatal Traffic Crashes

Traffic crashes are the leading cause of death in the United States for people aged 1 through 34 years (National Center for Health Statistics [NCHS] 1994). On average, 45,000 die annually in traffic crashes, and estimates indicate that alcohol is involved in as many as 43.6 percent of these deaths (National Highway Traffic Safety Administration 1994). The primary data source for fatal traffic crashes is the Department of Transportation's Fatal Accident Reporting System (FARS), an automated data bank on traffic crashes occurring in the United States in which a death occurs within 30 days of the crash.

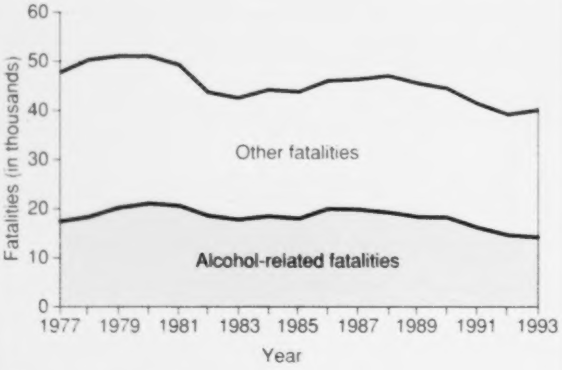
FARS records alcohol involvement in a traffic crash according to three variables: judgment of the investigating officer, blood alcohol concentration (BAC) test, and citation for driving under the influence (DUI). If one of these three variables is coded "yes," the crash is considered alcohol related. Data collected on alcohol-related crashes may be limited by the reluctance of police officers to report alcohol involvement based on their judgment, the inconsistent use of BAC tests, and the relatively few DUI citations given (Zobeck et al. 1994).

Figure 4 presents trends in alcohol-related versus non-alcohol-related traffic crash fatalities (Campbell et al. 1995). Although the two traffic fatality types appear roughly parallel, some recent differences are notable: In 1986, alcohol-related traffic deaths increased sharply by 11 percent, but non-alcohol-related traffic fatalities increased a modest 1 percent. Beginning in 1987, alcohol-related traffic crash fatalities declined each year, ending with a 17-year low in 1993, with 14,225 fatalities. A less stable trend occurred with non-alcohol-related traffic crash fatalities: Fatalities in this category increased in 1988 and 1993.

Among young drinking drivers (i.e., those 16 to 24 years old), the percentage of deaths from alcohol-related traffic crashes declined by 30 percent between 1977 and 1993, whereas the percentage of deaths among persons aged 25 to 44 years increased by 45 percent during this period. Of note is that persons aged 16 to 24 accounted for 28 percent of all drinking driver deaths in 1993 but constituted only 15 percent of all licensed drivers in the United States (Federal Highway Administration 1994). These statistics indicate that young drivers continue to be overrepresented in drinking driver deaths.

Statistics indicate that alcohol involvement and risk of death varies according to a person's role in the crash (Campbell et al. 1995). For example, in 1993, 42 percent of all driver deaths, 36 percent of all passenger deaths, and 12 percent of all nonoccupant deaths were alcohol related. In both alcohol-related or non-alcohol-related crashes, drivers were more likely to die than those in other roles, but drivers represented a larger proportion of fatalities in alcohol-related crashes than in non-alcohol-related crashes. Male drivers were more likely than female drivers to be involved in fatal traffic crashes, and alcohol involvement was about twice as high for male drivers as for female drivers.

Figure 4. Alcohol-related and other traffic crash fatalities, United States, 1977–1993.



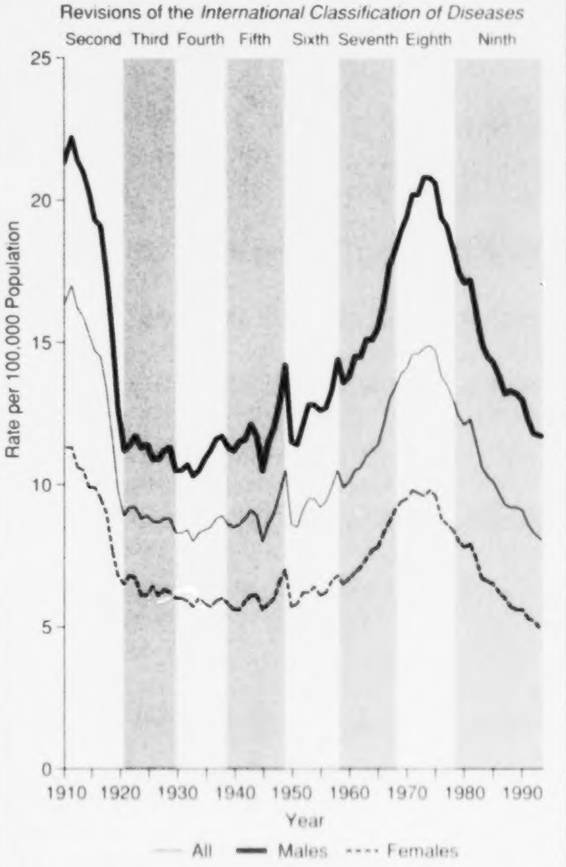
Source: Campbell et al. 1995.

Despite considerable progress in the prevention of alcohol-related traffic crashes, traffic fatalities associated with alcohol place a tremendous burden on society. Years of potential life lost (YPLL) is one way to calculate the human cost of premature death for a particular cause. This measure involves subtracting the age at death from 65 for each death and then summing the total across all deaths (Campbell et al. 1995). YPLL decreased 29 percent for men and 17 percent for women for all traffic crashes from 1977 to 1993. In 1993, approximately 40 percent of the YPLL for men and approximately 32 percent for women were attributable to alcohol-related crashes. The proportion of alcohol-related YPLL decreased by 1.9 percent for men and by 2.0 percent for women between 1992 and 1993.

Liver Cirrhosis Mortality

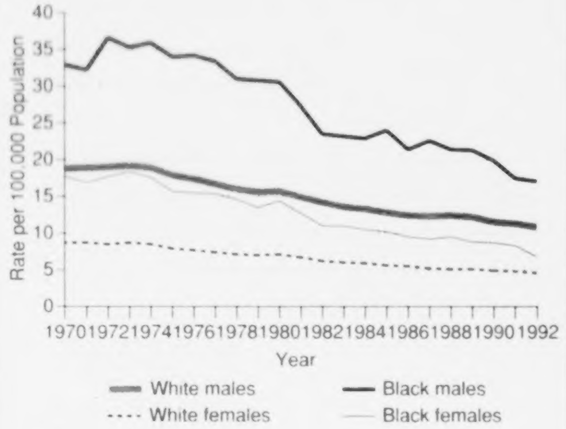
Liver cirrhosis is a grave and irreversible condition that accounted for 25,407 deaths in the United States in 1992, making it the 11th leading cause of death (DeBakey et al. 1995). Cirrhosis is characterized by a progressive replacement of healthy liver tissue with diffuse scarring, leading to liver failure and death. Data on liver cirrhosis mortality are compiled by national death records collected annually by the NCHS. Because alcohol consumption is a significant risk factor for cirrhosis, data are discussed for all cirrhosis deaths as well as for those specifically coded as alcohol related. The most recent year for which data are complete is 1992.

Figure 5a. Age-adjusted death rates of liver cirrhosis by gender: death registration States, 1910–1932, and United States, 1933–1992.



Source: DeBakey et al. 1995

Figure 5b. Age-adjusted death rates of liver cirrhosis (ICDA-8: all 571) by gender and race, United States, 1970–1992.



Source: DeBakey et al. 1995.

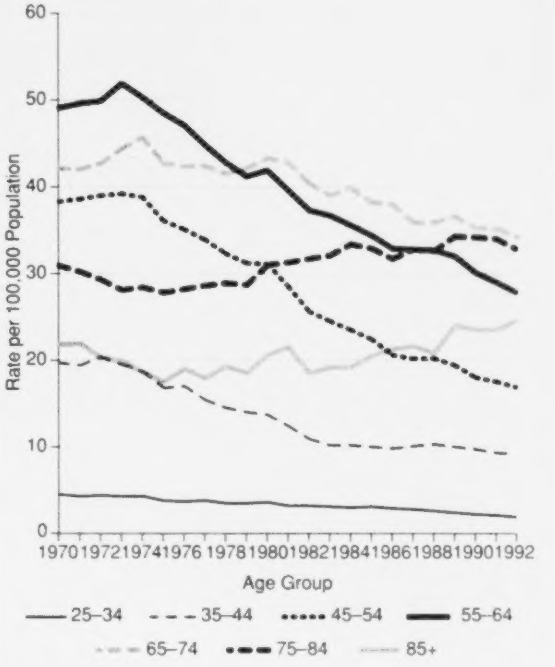
Deaths from liver cirrhosis began to increase gradually after the repeal of Prohibition in 1933, peaking in 1973 at an age-adjusted rate of 14.9 per 100,000 population (figure 5a) (DeBakey et al. 1995). Between 1973 and 1991, rates declined steadily, and by 1992, the age-adjusted cirrhosis death rate had dropped to 8.1 per 100,000 population. Age-adjusted death rates between 1910 and 1992 were consistently about twice as high for men as for women.

Figure 5b presents age-adjusted death rates for cirrhosis by gender and race for 1970 through 1992. All four groups studied experienced declining death rates, with decreases of 29.8 percent, 15.3 percent, 47.9 percent, and 33.3 percent for black males, white males, black females, and white females, respectively (DeBakey et al. 1995). Despite this progress, the risk of death from alcohol-related cirrhosis remains greater for men than for women and greater for blacks than for whites. Although the death rate among black males was 73.8 percent greater than that among white males in 1992, the gap between males of different races narrowed during the 22-year study period (1970–1992) because of a prominent decline in the death rate for black men.

Review of age-specific cirrhosis deaths rates between 1970 and 1992 indicated that, with the exception of adults aged 75 years and older, rates have dropped significantly for all age groups (figure 5c). However, among people aged 75 to 84 years, the death rate has increased by 6.5 percent; among those aged 85 and older, the rate has increased by 12.4 percent (DeBakey et al. 1995).

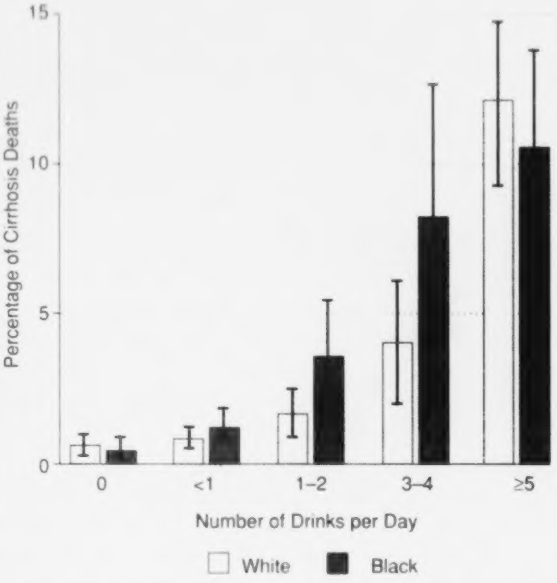
Although the decline in cirrhosis mortality is consistent with the previously reported decreases in per capita alcohol consumption, it is not clear whether changes in per capita consumption can account for all the variability in mortality rates from cirrhosis. For example, per capita consumption modestly declined from the mid-1970s to the mid-1980s while mortality rates during this period dropped rapidly. Mann et al. (1988, 1991) have suggested that treatment factors, such as increases or changes in treatment for alcohol problems, may have contributed to the decline. A literature review concluded that improvements in cirrhosis treatment and management likely were not associated with declining cirrhosis mortality rates, yet factors such as improvements in nutrition and prevention may have been involved (Smart and Mann 1991).

Figure 5c. Age-specific death rates of liver cirrhosis (ICDA-8: all 571), United States, 1970–1992.



Source: DeBakey et al. 1995.

Figure 6. Percentage of cirrhosis deaths of all decedents according to number of drinks per day and race/ethnicity.



Source: Parrish et al. 1993. Reprinted with permission from *Journal of Studies on Alcohol*, vol. 54, pp. 450–456, 1993. Copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, Piscataway, NJ 08855.

Parrish et al. (1993) examined a 1-percent sample of deaths in the United States derived from the 1986 National Mortality Followback Survey. Of the 461 cirrhosis deaths identified, 334 cases had complete alcohol information from the next of kin that was obtained through mailed questionnaires. Deaths from any type of cirrhosis were more likely to be among heavy drinkers (three or more drinks per day on average). Furthermore, the percentage of very heavy drinkers (five or more drinks per day on average) was highest among deceased persons with alcoholic cirrhosis, a finding that held across ethnic groups. As figure 6 illustrates, among deceased persons who consumed five or more drinks per day, 10 percent had cirrhosis. No significant differences were observed between black and white decedents in any drinking category.

Cirrhosis death rates also have been compared internationally using data from WHO (Edwards et al. 1994). Tables 5 and 6 present death rates from cirrhosis for European countries, the Americas, and the Caribbean. Because these rates were standardized for the European population, the overall death rate per 100,000 population for the United States presented in table 6 is higher than rates reported earlier (i.e., 11.6 in 1990 in table 6 compared with 8.6 percent in DeBakey et al. 1995, figure 5a). Cirrhosis deaths in European countries (table 5) vary greatly, from a high of 54.8 cirrhosis deaths per 100,000 in Hungary to a low of 2.9 per 100,000 in Ireland. Rates of cirrhosis deaths also vary widely in the Americas and the Caribbean (table 6). Overall, the international data indicate that cirrhosis is found in all countries and that the variability in cirrhosis death rates among countries cannot be explained by any one variable (e.g., beer- versus wine-drinking countries or average alcohol consumption levels) (Smart and Mann 1992).

Alcohol-Related Morbidity

Data on alcohol-related morbidity are important for policymakers, health care providers, and alcohol researchers. Since 1979, such data have been gathered through a series of National Hospital Discharge Surveys (NHDSs), which have used a sample of non-Federal, short-stay hospitals having six or more beds and an average length of stay under 30 days. Survey reports

Table 5. Deaths in Europe from cirrhosis per 100,000 living, with age standardization for European population and ranking from highest to lowest incidence.*

Country	Year of Report	Total	Standardized Mortality: Males	Standardized Mortality: Females	Standardized Mortality: M/F Ratio
Hungary	1991	54.8	79.7	32.6	2.4
Romania	1991	38.1	47.5	28.8	1.6
Germany, former Democratic Republic of	1991	33.7	47.9	19.4	2.5
Austria	1992	28.2	41.2	16.4	2.5
Portugal	1993	26.9	39.3	15.1	2.5
Italy	1990	26.8	31.7	18.0	1.8
Czechoslovakia	1991	25.1	38.1	13.4	2.8
Germany, Federal Republic of	1991	22.2	30.4	14.6	2.1
Spain	1989	21.0	30.0	12.9	2.3
Luxembourg	1991	18.7	21.9	15.4	1.4
Former Yugoslavia	1990	18.4	27.7	10.2	2.7
France	1991	17.0	23.3	10.6	2.2
Bulgaria	1991	15.0	22.0	07.8	2.8
Poland	1991	13.9	19.1	09.2	2.1
Belgium	1987	11.9	14.4	09.5	1.5
Finland	1992	10.7	15.3	04.2	3.6
Switzerland	1991	09.5	12.9	06.1	2.1
Malta	1991	09.0	14.0	03.9	3.6
Greece	1990	08.9	12.1	05.8	2.1
Israel	1989	08.7	10.3	07.0	2.5
Sweden	1990	06.8	08.8	04.7	1.9
United Kingdom	1991	06.1	06.9	05.3	1.3
Netherlands	1991	05.1	06.3	03.9	1.6
Norway	1991	04.4	05.4	03.3	1.6
Ireland	1990	02.9	03.1	02.7	1.1

*Statistics supplied by the World Health Organization, Geneva.

Source: Edwards et al. 1994. Reprinted from *Alcohol Policy and the Public Good* 1994 by permission of Oxford University Press.

include only those patients with diagnoses *directly* caused by alcohol use; diseases or injuries indirectly attributable to alcohol are not considered. Rates may reflect multiple discharges for patients hospitalized more than once in the same year.

In 1993, an alcohol-related diagnosis was listed first in the medical records (e.g., first-listed diagnosis) for approximately 429,000 (1.5 percent) of the discharge episodes from short-stay hospitals for persons aged 15 years and older (Caces et al. 1995). The majority (61 percent) of these diagnoses was for alcohol dependence syndrome, followed by cirrhosis (18 percent), alcoholic psychoses (15 percent), and nondependent abuse of alcohol (6 percent). The relative ranks of these diagnoses remained fairly stable between 1979 and 1993, with the exception of 1987, when alcohol psychosis diagnoses exceeded cirrhosis diagnoses.

Although the percentage of alcohol-related first-listed diagnoses has changed little between 1979 and 1993, the percentage of alcohol-related all-listed diagnoses (e.g., an alcohol-related diagnosis in any of the seven possible diagnostic fields in the medical records) has increased. How much of this increase is real and how much of it may be due to a greater awareness of alcohol-related problems by health care professionals is unclear.

During the time period studied, a growing fraction of alcohol-related diagnoses was not first-listed. Over the 15-

Table 6. Deaths in the Americas and the Caribbean from cirrhosis per 100,000 living, with age standardization for European population and ranking from highest to lowest incidence.*

Country	Year of Report	Total	Standardized Mortality		
			Males	Females	M/F Ratio
Mexico	1990	48.6	72.5	21.8	03.3
Chile	1989	46.2	67.5	26.5	02.5
Puerto Rico	1990	29.7	47.2	13.5	04.0
Ecuador	1988	21.7	28.7	14.1	02.0
Costa Rica	1989	20.4	26.7	13.1	02.0
Venezuela	1989	19.4	28.6	09.6	03.0
Argentina	1989	13.3	20.1	06.4	03.1
Trinidad and Tobago	1989	13.2	19.6	06.7	02.9
Cuba	1990	12.4	13.3	11.3	01.2
Panama	1987	11.6	14.2	07.7	01.8
United States of America	1990	11.6	15.2	08.0	01.9
Uruguay	1990	11.5	17.5	06.8	02.6
Canada	1990	09.3	12.7	05.8	02.2

*Statistics supplied by the World Health Organization, Geneva.
Source: Edwards et al. 1994. Reprinted from *Alcohol Policy and the Public Good* 1994 by permission of Oxford University Press.

year period, 48 percent of alcohol-related diagnoses were first-listed, whereas "hidden" alcohol diagnoses increased from 39 percent in 1979 to 65 percent in 1993.

Of note are the limitations of the NHDS data base. For example, the Department of Veterans' Affairs and other Federal hospitals are excluded from the survey, as are hospitals having an average length of stay of 30 days or greater. Also not included in the sample are individuals having alcohol-related conditions for which hospitalization does not occur. Finally, bias stemming from health care professionals' relative willingness to report alcohol-related morbidity may influence the estimates.

Hospital discharge data may underestimate the prevalence of alcohol use disorders among hospitalized persons. For example, in a study by Umbricht-Schneiter et al. (1991), patients admitted to a large teaching hospital were screened (using the CAGE and short version of the Michigan Alcoholism Screening Test, or SMAST, instruments)[3] for alcohol problems, and the results were compared to the patients' discharge summaries. According to the discharge data, only 1.4 percent of the patients had a primary and 6 percent had a secondary (but no primary) alcohol-related diagnosis. Another 15 percent of the patients, however, had screened positive for an alcohol problem on admission, but there was no mention of an alcohol-related problem on these patients' discharge records. That is, the discharge data indicated that 7.4 percent of the patients had alcohol-related problems but 22.4 percent was suggested by the screening data. Screening instruments are used to detect potential or developing alcohol problems in individuals, and the instruments used do not differentiate between current and past alcohol problems. However, the investigators concluded from the study that routine screening of hospitalized persons for alcohol problems could improve medical care or enable the use of prevention approaches.

Social and Other Consequences

Because of the decrease in per capita consumption, the decrease in the proportions of people reporting heavier drinking patterns, and the downward shifts in alcohol-related traffic crashes and liver cirrhosis deaths, it is important to consider what, if any, changes have occurred in reports of social and other consequences related to alcohol use. Alcohol abuse can contribute to a variety of social, legal, and occupational problems. Researchers frequently use surveys to assess such alcohol-related problems. Surveys can be used to evaluate the frequency

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[3] For a more detailed review of these screening instruments, see the *Eighth Special Report to the U.S. Congress on Alcohol and Health.*

Table 7. Dependence symptoms and social consequences by demographic characteristics among current drinkers only (in percent)[*][†] in 1984 and 1990.

	3+ Dependence Symptoms				2+ Social Consequences			
	1984		1990		1984		1990	
	%	N[‡]	%	N[‡]	%	N[‡]	%	N[‡]
Gender								
Male	08.8	437	09.9	392	15.0	439	16.1	392
Female	04.3	414	05.1	356	06.6	415	09.2	356
Age, years								
18–29	10.1	282	15.3	223	16.9	283	25.9	223[§]
30–39	06.8	203	04.7	189	10.0	203	09.6	189
40–49	06.5	121	07.0	124	11.7	122	11.5	124
50–59	02.8	99	03.4	79	05.8	99	03.9	79
60+	02.6	144	02.0	133	03.5	144	01.9	133
Marital Status								
Married/LWS	05.1	543	04.5	477	09.5	544	08.7	477
Separated	14.2	21	02.6	24	11.5	21	07.2	24
Divorced	06.4	62	09.0	60	11.7	62	15.1	60
Widowed	04.0	46	03.1	35	04.3	46	04.0	35
Never married	11.3	180	18.8	151	16.6	181	27.6	151[§]
Ethnicity								
Black	08.6	79	09.3	90	12.6	78	21.8	90
White	06.5	711	06.9	563	10.5	712	11.2	563
Hispanic	05.4	44	12.2	67	09.4	44	16.2	67
Other	05.2	17	04.9	28	22.8	17	06.7	28
Income								
Above median	05.1	451	05.2	411	10.5	451	09.3	411
Below median	08.8	349	10.3	295	11.4	350	17.2	295
Employment								
Full time	06.9	502	07.5	445	12.1	504	13.5	445
Part time	06.7	93	03.0	91	11.0	93	10.1	91
Retired	03.0	92	02.9	88	03.1	92	02.3	88
Homemaker	05.6	91	02.3	52	09.0	91	04.0	52
Other	10.8	74	23.5	72[§]	14.8	74	30.8	72[§]
Religion								
Catholic	05.1	268	07.3	236	08.8	269	11.4	236
Jewish	01.8	26	06.9	19	00.0	26	00.0	19
Liberal Protestant	05.3	160	04.0	142	07.8	161	09.3	142
Conservative Protestant	06.6	292	07.2	248	11.8	292	14.9	248
Other	14.4	103	15.1	87	21.9	103	17.6	87
Importance of Religion								
Very	04.1	366	05.0	308	06.5	367	09.1	308
Somewhat	07.8	348	08.2	321	13.3	348	16.6	321
Not really	10.8	88	12.8	78	14.3	88	13.6	78
Not at all	10.1	35	13.1	38	23.2	35	09.6	38

[*] Both percentages and N's are weighted.

[†] National Alcohol Survey 1990.

[‡] N's vary slightly because of missing data.

[§] Difference between 1984 and 1990 is significant at 0.05 level by two-tailed test of significance of difference of proportions.

Table 7. Dependence symptoms and social consequences by demographic characteristics among current drinkers only (in percent)*† in 1984 and 1990 *(continued).*

	3+ Dependence Symptoms				**2+ Social Consequences**			
	1984		**1990**		**1984**		**1990**	
	%	N‡	%	N‡	%	N‡	%	N‡
Education								
Less than high school	09.7	166	12.5	136	13.8	166	17.8	136
High school graduate	09.0	319	06.7	293	12.8	319	14.5	293
Some college	03.7	194	08.5	156	08.1	195	13.3	156
College graduate	02.8	173	04.3	162	07.9	173	05.0	162
Urbanicity								
Metropolitan area ≥50,000 population	07.9	296	09.7	337	13.9	297	13.5	337
Metropolitan area ≤50,000 population	06.3	196	05.6	232	09.0	196	10.7	232
Nonmetropolitan area	05.8	359	06.4	179	09.5	360	14.2	179
Region								
Northeast	05.6	219	04.3	169	08.1	216	09.5	169
Midwest	05.9	232	07.4	194	07.9	233	12.2	194
Pacific	09.2	124	11.1	97	13.8	124	11.4	97
South	06.3	238	08.5	243	13.9	238	14.9	243
Mountain	10.7	42	08.1	44	16.1	42	18.9	44

Source: Midanik and Clark 1995. Reprinted with permission from *Journal of Studies on Alcohol*, vol. 56, pp. 395–402, 1995. Copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, Piscataway, NJ 08855.

and amount of alcohol a person consumes and how drinking affects employment and family obligations, behavior and mood, and encounters with others.

The NAS, conducted by the Alcohol Research Group, included questions to identify whether respondents were experiencing social and other consequences (e.g., problems with friends, family, and spouses; fighting; problems at work; difficulties with police; financial problems; loss of control over drinking; binge drinking; and alcohol-related health problems or accidents) from their drinking. Using data from the 1984 and the 1990 NAS, Midanik and Clark (1995) compared reports of dependence symptoms and social consequences during the past year. Overall, the two surveys reported similar rates of these problems among current drinkers in the general population. Three or more dependence symptoms (of 13 items) were reported by 6.7 percent of current drinkers in 1984 and 7.6 percent in 1990. Two or more social consequences (of 21 items) were reported by 10.9 percent of current drinkers in 1984 and 12.8 percent in 1990.

Within demographic subgroups (table 7), none of the proportions for dependence symptoms or social consequences was significantly lower in 1990 than in 1984. Indeed, significant increases in reports of two or more social consequences were found for younger people (18 to 29 years old), persons who had never married, and respondents who were not employed.[4] Furthermore, the proportion of unemployed respondents reporting three or more dependence symptoms was significantly higher in 1990 than in 1984.

To assess the relationship between drinking pattern variables and alcohol-related problems during the past 12 months, Midanik and Clark (1995) conducted separate statistical analyses for dependence symptoms and social consequences while controlling for demographic variables. Analyses were conducted with and without two measures of alcohol use: volume of alcohol consumed per day and frequency of drunkenness (i.e., getting drunk once a month or more versus getting drunk less than once a month). When both alcohol use variables were entered into the analysis, only younger age (18 to 29 years) predicted alcohol problems.

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[4] This category included respondents who were retired, homemakers, or not employed full time or part time.

Whereas Midanik and Clark (1995) assessed drinking problems during the past 12 months, Chou and Pickering (1992) assessed the effects of early onset of drinking as a predictor of lifetime alcohol-related problems using the 1988 NHIS data set. Respondents were asked questions on nine separate lifetime groups of symptoms corresponding to the DSM-III-R. The prevalence of experiencing three or more symptom groups during a person's lifetime was 42.4 percent. Moreover, for nearly all race, gender, and age subgroups in the survey, significantly higher risks for three or more lifetime symptom groups were reported for people who began drinking at 15 years of age or earlier.

Midanik and Clark (1995) noted that despite the decreases in alcohol consumption, specific drinking patterns, and liver cirrhosis mortality, no overall changes in reports of dependence symptoms or social consequences were found from the 1984 and 1990 NAS data. However, significant increases were found in a specific subgroup of the population: younger persons who had never married and who were neither employed, retired, nor homemakers. Midanik and Clark offered two reasons why overall reports of drinking problems have not declined. First, as Room (1991) suggests, patterns of increasing and decreasing alcohol use occur across societies. With these patterns, per capita consumption and alcohol problems increase for a long period of time, followed by a period in which alcohol use is discouraged by changes in laws and less formal controls. Midanik and Clark (1995) suggest that the United States may be at the beginning of a period of declining consumption and that a decline in alcohol problems may occur after a "lag" time. Second, the investigators propose that the proliferation of prevention efforts in the 1980s, which sometimes used the media to carry the message that harmful drinking is dangerous, helped to increase the public's awareness of a wider range of alcohol-related problems.

Alcohol Use as a Risk for Social Consequences

Another approach to assessing the relationship between alcohol use and social consequences is to examine the probability of occurrence of specific consequences (or types of consequences) at given levels of alcohol use. This approach, called risk-function analysis, is not new to the alcohol field but has been used primarily in assessing the chronic, physical effects of alcohol use (Edwards et al. 1994). More recently, it has been applied to both positive social experiences (e.g., improved ability to express feelings, to converse, and to sort out job-related problems) and negative social consequences (e.g., drunk driving, job difficulties, and interpersonal problems) of drinking (Hauge and Irgens-Jensen 1986, 1987, 1990; Mäkelä and Mustonen 1988; Mäkelä and Simpura 1985). The relationship between alcohol consumption and specific consequences can take several forms, such as an exponential function of the consumption level (e.g., risk of cirrhosis) or a U-shaped or J-shaped curve (e.g., coronary heart disease).

The risk function for social consequences also may vary by type of problem and by culture (Mäkelä and Mustonen 1988). Risk-function analysis allows researchers to assess, for example, whether reports of specific types of consequences associated with drinking show an even increase across the range of average daily volume categories or whether an effect is negligible below a certain volume of alcohol consumed. Furthermore, the frequency with which a person engages in heavier drinking per occasion and its relationship to specific drinking problems can be evaluated.

Earlier studies of the relationship between the shape of risk curves, alcohol use, and social consequences were conducted in the Scandinavian countries. For example, Mäkelä and Simpura (1985) used data from a representative sample of adults in Finland in 1979 to assess the probability of specific types of consequences as a funcion of annual alcohol intake. They found that the probability of particular alcohol-related behaviors (e.g., belligerence and drunk driving) and consequences (e.g., accidents and health problems) tends to increase less quickly with increasing consumption than the probability of social reactions to drinking. They also reported that at all levels of consumption, reported positive effects were more common than worries or negative reactions to drinking. At the highest level of consumption, approximately the same number of drinkers reported being worried about their drinking as reported getting benefits from it. Furthermore, informal social reactions and personal concerns about drinking began to occur at much higher levels than did reactions from institutional agents (e.g., police, doctors, work supervisors, and colleagues). As consumption increased, however, reactions from institutional agents occurred more frequently.

Recently, risk-function analyses have been undertaken in Canada and the United States. Using a national sample of Canadians aged 15 years and older, Room et al. (1995) assessed risk curves for alcohol use and harm to six life areas from a person's own drinking and for assault by another drinker. For both types of problems, the investigators found that the probability of harm rose steadily with the respondent's volume of drinking; no clear lower threshold of drinking at which an individual can be "completely safe" was noted. However, at any specific volume of alcohol use, heavier use patterns (five or more drinks on one occasion) greatly increased the probability of harm.

In a similar type of risk analysis using the 1988 NHIS data, Midanik et al. (in press) examined alcohol use (number of drinks in the last year and number of days drinking five or more drinks) with self-reports of work problems and drunk driving. The results indicated that even at lower levels of drinking (average of one drink or less per day), there is still some degree of risk for work problems and driving. However, risks of both problems at lower and moderate-level drinking was significantly higher for respondents who had five or more drinks during 1 day at least once in the last year. This finding was similar to that from the Canadian research (Room et al. 1995).

On the basis of a literature review summarizing a person's drinking and degree of risk, Edwards et al. (1994) argued that "[The] complexities are real, but the messages that emerge from the evidence . . . are for the individual and society outstandingly clear—less is better, more drinking carries more risk for a wide range of adverse happenings, and heavy drinking is a distinctly dangerous behavior" (p. 68).

Alcohol Abuse and Alcohol Dependence

Since the publication of the 1993 *Eighth Special Report to the U.S. Congress on Alcohol and Health*, researchers have conducted additional studies on the prevalence of alcohol use disorders in the United States. Many of these studies have compared prevalence by using different survey data and diagnostic criteria (Caetano and Room 1994; Caetano and Tam 1995; Grant et al. 1992, 1994; Kessler et al. 1994).

Table 8 presents 1-year prevalence rates for alcohol abuse and dependence for four national surveys (NHIS 1988, NAS 1990, National Comorbidity Survey 1992, and National Longitudinal Alcohol Epidemiologic Survey [NLAES] 1992). Although each of the four national surveys assessed alcohol use disorders, the specific wording

Table 8. One-year prevalence of alcohol abuse and dependence (AAD) combined and alcohol dependence (DEP), reported by all national studies, in percent, by gender.

	Men		Women		Total	
	AAD	DEP	AAD	DEP	AAD	DEP
National Health Interview Survey (1988)[*]						
DSM-III-R[†]	13.4	09.6	04.4	03.2	08.6	06.3
DSM-IV	09.3	09.2	03.0	03.0	06.0	05.9
National Alcohol Survey (1990)						
DSM-III-R	†	05.3	‡	01.7	‡	03.2
DSM-IV	‡	05.7	‡	02.2	‡	03.9
ICD-10	‡	07.8	‡	03.4	‡	05.4
National Comorbidity Survey (1992)						
DSM-III-R	‡	‡	‡	‡	09.7	07.2
National Longitudinal Alcohol Epidemiologic Survey (1992)						
DSM-IV	11.0	06.3	04.1	02.6	07.4	04.4

[*] National Health Interview Survey (Grant et al. 1992); National Alcohol Survey (Caetano and Room 1994; Caetano and Tam 1995); National Comorbidity Survey (Kessler et al. 1994); National Longitudinal Alcohol Epidemiologic Survey (Grant et al. 1994).

[†] DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

[‡] Data not published.

of items that composed each component of abuse and dependence differed among the surveys.

To compare the prevalence of alcohol abuse and dependence by using both DSM-III-R and the "proposed DSM-IV" diagnostic criteria, Grant et al. (1992) used the 1988 NHIS sample and assessed rates for various subtypes of dependence. The authors examined the prevalence rates according to DSM-III-R and DSM-IV by disaggregating the criteria to reflect several subtypes (e.g., alcohol dependence with abuse and without abuse, and alcohol abuse without dependence). They found that DSM-IV produced lower prevalence estimates for the combined diagnosis of alcohol abuse and dependence than did DSM-III-R (6.00 percent and 8.63 percent, respectively); this finding held for both men and women. In contrast, when prevalence rates of alcohol dependence were compared, the differences between the two versions of the DSM were less marked: Prevalence estimates of alcohol dependence was 6.25 percent for DSM-III-R and 5.93 percent for DSM-IV. These estimates were fairly similar for men and women.

Using data from the 1990 NAS, Caetano and Room (1994) compared prevalence rates for alcohol dependence based on criteria from the DSM-III-R, DSM-IV, and ICD-10. The investigators found a higher prevalence estimate from ICD-10 (5.4 percent) than from DSM-III-R (3.2 percent). DSM-IV-based prevalence estimate for alcohol dependence fell between the other two estimates (3.9 percent) (Caetano and Tam 1995).

Alcohol abuse and dependence estimates derived from the National Comorbidity Survey were based on a structured psychiatric interview using DSM-III-R diagnostic criteria in a national probability sample of 8,098 respondents 15 to 54 years old in the United States. Kessler et al. (1994) found that 7.2 percent of the sample met the criteria for a diagnosis of alcohol dependence based on the DSM-III-R, whereas 2.5 percent met the criteria for alcohol abuse without dependence (9.7 percent were classified as alcohol abusers or alcohol dependent combined).

More recently, data on the prevalence of DSM-IV alcohol abuse and dependence from the 1992 NLAES were published (Grant et al. 1994) (table 9). This study involved a large multistage design of the U.S. household population, yielding a sample size of 42,861 respondents 18 years of age and older. Blacks and young adults (18 to 29 years old) were oversampled. Grant et al. (1994) reported a combined prevalence rate of alcohol abuse or alcohol dependence of 7.4 percent (13,760 respondents). This prevalence rate is higher than that reported in the 1988 NHIS (6.0 percent), which was based on a then-proposed DSM-IV criteria. According to NLAES data, the percentage of respondents who were alcohol dependent was 4.4 percent, which was higher than that reported in the 1990 NAS (3.9 percent) and lower than that reported in the 1988 NHIS (5.9 percent).

To assess further the relationship of alcohol consumption and alcohol dependence, Midanik et al. (in press) constructed risk curves for alcohol use (number of drinks in the last year and drinking five or more drinks in 1 day at least once in the last year) and reports of alcohol dependence (based on diagnostic criteria) in the 1988 NHIS. They found that the overall relationship between ICD-10 alcohol dependence and volume were generally linear and very similar for men and women. To assess the interaction of drinks per day and heavier drinking patterns, a risk curve was derived for volume and ICD-10 alcohol dependence for respondents who had and had not reported drinking five or more drinks on any occasion during the year. At each volume level, there are clear, significant differences between the two curves, with respondents who drank five or more drinks on any occasion having higher rates of ICD-10 alcohol dependence.

Special Population Groups

Women

In general, research comparing women's and men's drinking patterns has yielded two consistent findings: Women drink less and report fewer alcohol-related problems than men do (Wilsnack and Wilsnack 1995). Recent findings from the 1990 NAS confirmed that women drink less (Midanik and Clark 1994). Compared with men, fewer women were current drinkers, weekly drinkers, and drinkers of five or more drinks on one occasion at least weekly (see table 3). In their analysis of the 1988 NHIS, Dawson and Archer (1992) found similar results and also reported that men's average daily alcohol intake was about twice as high as that of women. When differences in body weight and composition were considered, the ratio of male-to-female consumption was reduced. Dawson and Archer (1992) strongly recommended adjusting for body water when conducting research on the health or performance consequences of alcohol consumption.

Table 9. Prevalence and population estimates* of DSM-IV alcohol abuse and dependence by age, gender, and ethnicity, United States, 1992.

Ethnicity/ Gender/ Age, years	Alcohol Abuse Only			Alcohol Dependence Only			Alcohol Dependence With Abuse			Total Alcohol Abuse and Dependence		
	Prevalence %	S.E.	Population Estimate	Prevalence %	S.E.	Population Estimate	Prevalence %	S.E.	Population Estimate	Prevalence %	S.E.	Population Estimate
Nonblack Males	4.93	(0.21)	3,928	2.10	(0.14)	1,673	4.30	(0.21)	3,423	11.33	(0.34)	9,024
18–29	10.02	(0.58)	2,031	3.91	(0.34)	792	9.55	(0.55)	1,935	23.48	(0.84)	4,758
30–44	4.81	(0.30)	1,308	2.01	(0.23)	546	4.07	(0.32)	1,107	10.89	(0.47)	2,961
45–64	2.51	(0.31)	521	1.44	(0.22)	300	1.66	(0.25)	346	5.61	(0.44)	1,167
65+	0.60	(0.19)	69	0.31	(0.09)	36	0.30	(0.09)	35	1.21	(0.23)	140
Black Males	2.50	(0.43)	237	2.48	(0.39)	235	3.27	(0.42)	310	8.25	(0.72)	782
18–29	3.97	(0.92)	116	3.92	(0.99)	115	4.44	(1.01)	130	12.33	(1.70)	361
30–44	2.78	(0.78)	96	2.58	(0.65)	89	3.39	(0.71)	117	8.75	(1.21)	302
45–64	1.17	(0.58)	25	1.12	(0.35)	24	2.90	(0.72)	62	5.19	(0.97)	111
65+	0.00	(0.00)	0	0.74	(0.50)	7	0.08	(0.08)	1	0.82	(0.51)	8
Total Males	4.67	(0.19)	4,165	2.14	(0.13)	1,908	4.19	(0.19)	3,733	11.00	(0.32)	9,806
18–29	9.26	(0.52)	2,147	3.91	(0.34)	907	8.90	(0.50)	2,065	22.07	(0.77)	5,119
30–44	4.58	(0.28)	1,404	2.07	(0.21)	635	4.00	(0.29)	1,225	10.65	(0.45)	3,264
45–64	2.38	(0.28)	546	1.41	(0.20)	324	1.78	(0.24)	408	5.57	(0.41)	1,278
65+	0.55	(0.18)	69	0.34	(0.09)	43	0.29	(0.08)	36	1.18	(0.22)	148
Nonblack Females	1.62	(0.11)	1,379	1.20	(0.10)	1,019	1.43	(0.10)	1,216	4.25	(0.20)	3,614
18–29	4.29	(0.34)	851	2.60	(0.28)	515	4.10	(0.35)	814	10.99	(0.64)	2,180
30–44	1.58	(0.17)	428	1.23	(0.15)	335	1.13	(0.15)	307	3.94	(0.27)	1,070
45–64	0.42	(0.10)	93	0.68	(0.14)	149	0.35	(0.07)	75	1.45	(0.19)	317
65+	0.04	(0.03)	7	0.13	(0.06)	20	0.12	(0.07)	20	0.29	(0.09)	47
Black Females	0.71	(0.16)	84	1.30	(0.21)	153	0.87	(0.18)	102	2.88	(0.32)	339
18–29	1.24	(0.42)	43	1.70	(0.41)	59	0.38	(0.15)	13	3.32	(0.60)	115
30–44	0.98	(0.30)	40	1.18	(0.33)	48	2.02	(0.49)	83	4.18	(0.65)	171
45–64	0.02	(0.02)	0	1.70	(0.52)	45	0.20	(0.12)	5	1.92	(0.54)	50
65+	0.00	(0.00)	0	0.00	(0.00)	0	0.00	(0.00)	0	0.00	(0.00)	0
Total Females	1.51	(0.10)	1,463	1.21	(0.09)	1,172	1.36	(0.09)	1,318	4.08	(0.18)	3,953
18–29	3.83	(0.30)	894	2.46	(0.25)	574	3.55	(0.30)	827	9.84	(0.56)	2,295
30–44	1.50	(0.15)	469	1.23	(0.14)	383	1.25	(0.15)	391	3.98	(0.25)	1,243
45–64	0.38	(0.09)	93	0.79	(0.14)	194	0.33	(0.07)	81	1.50	(0.18)	368
65+	0.04	(0.03)	7	0.12	(0.05)	20	0.11	(0.06)	20	0.27	(0.09)	47
Total	3.03	(0.11)	5,628	1.66	(0.08)	3,080	2.72	(0.11)	5,052	7.41	(0.20)	13,760
18–29	6.54	(0.33)	3,041	3.18	(0.21)	1,481	6.22	(0.30)	2,893	15.94	(0.53)	7,415
30–44	3.02	(0.16)	1,873	1.64	(0.13)	1,018	2.61	(0.17)	1,615	7.27	(0.26)	4,506
45–64	1.35	(0.15)	639	1.09	(0.12)	518	1.03	(0.12)	488	3.47	(0.22)	1,645
65+	0.25	(0.08)	75	0.21	(0.05)	63	0.18	(0.05)	55	0.64	(0.10)	193

*All population estimates are in thousands.

Note: Components may not always sum to the totals displayed in the table because of rounding.

Source: Grant et al. 1994.

Using the same data, Dawson (1993) assessed the effects of beverage preference on drinking patterns for men and women. When beverage preference was considered, the author found no meaningful differences in drinking patterns between men and women with similar levels of alcohol intake. This result does not support the view that the differences in alcohol consumption between men and women are due to men drinking more per occasion. Dawson (1993) suggests that apparent differences in drinking patterns are due to differences in preferred beverage.

Data from the Behavioral Risk Factor Surveillance System in 1991 provide a source of information on drinking patterns for women of childbearing age (Centers for Disease Control and Prevention 1994).

A telephone survey of 26,819 women 18 to 44 years old that assessed drinking patterns in the last month indicated that 50 percent of the women were nondrinkers, 45 percent were light drinkers (≤30 drinks in the past month), 3 percent were moderate drinkers (31 to 59 drinks in the past month), and 2 percent were heavy drinkers (≥60 drinks in the past month). Among all drinkers, 21 percent reported having five or more drinks on one occasion during the last month. Of the 1,067 pregnant respondents, 1.3 percent reported drinking five or more drinks on one occasion at least once in the last month. When the prevalence of frequent drinking was ranked by region, a higher prevalence was found among women of childbearing age in the northern regions of the United States than in other regions. The authors argued that these results indicate the need for ongoing surveillance of alcohol consumption patterns and the continued need to target women of childbearing age for education about alcohol use during pregnancy. (See Chapter 6, Effects of Alcohol on Fetal and Postnatal Development, for a review of these effects.)

In terms of alcohol-related problems, fewer women respondents to the 1984 NAS than to the 1990 NAS (see table 7) reported three or more dependence symptoms and two or more social consequences (Midanik and Clark 1995). Table 8 compares the gender-specific rates of alcohol abuse and alcohol dependence reported for all recent national studies. In most cases, the rates for men were at least twice that of women.

An important issue emerges concerning how women's drinking patterns may have changed over time: Several reviews have focused on trends in overall drinking and problem drinking in U.S. women (Wilsnack and Wilsnack 1995), alcohol use and older women (Wilsnack et al. 1995), and the implications for preventing women's drinking over time (Wilsnack in press). By assessing the literature on women's drinking over 20 years (1971–1991), Wilsnack and Wilsnack (1995) strongly argue that public perceptions and media reports based on available empirical evidence of an "epidemic" increase in women's drinking and a convergence of male and female drinking patterns were unfounded. An analysis of nine surveys conducted between 1971 and 1981 when per capita consumption in the United States was increasing (and at its peak in 1980 and 1981) revealed that women's drinking was relatively stable throughout this period. Furthermore, there was no evidence of convergence in rates of drinking or heavier drinking for men and women.

In an extended analysis of 15 U.S. national surveys, Wilsnack and Wilsnack (1995) drew several conclusions. First, women's drinking declined during the 1980s. Second, some drinking patterns declined more than others; for example, rates of heavy drinking (averaging 1 or more ounces of alcohol per day) significantly decreased across most age groups, whereas rates of abstention did not decrease. Third, increases in reports of rates of intoxication (feeling drunk) and decreases in reported episodes of heavy drinking among younger women are suggestive of cultural or cohort changes concerning how women perceive their drinking and the effects of alcohol. Fourth, declines in women's drinking during the 1980s were less marked than the consistent and sharp decreases reflected in apparent per capita consumption rates over the same period.

Wilsnack and Wilsnack (1995) also identified several personal and environmental factors that may increase women's risks of problem drinking. These factors are the influence of husbands' or partners' drinking; the relationship of depression and alcohol abuse or dependence in women; sexual experience, including alcohol expectancies and reported effects of drinking on sexual behavior, sexual orientation, and sexual dysfunction; and violent victimization, including physical and sexual victimization in childhood as well as in adulthood.

Youth

Several data sources have been used to assess alcohol use among young people. Since the mid-1970s, annual national surveys of secondary school students, supplemented by followups for students 18 to 30 years of age, have been conducted. These surveys compose the *Monitoring the Future* studies (Johnston et al. 1995, 1996), which are reported separately for high school seniors and for college students and young adults.

Johnston et al. (1995, 1996) reported that although purchase of alcohol is illegal for all high school students and most undergraduate college students, most have had experience with alcohol: According to 1994 survey data, approximately 56 percent of 8th graders have tried alcohol, as have 71 percent of 10th graders, 80 percent of 12th graders, and 80 percent of college students. For heavy drinking (five or more drinks in a row at least once in the prior 2 weeks), the rates are lower but remain substantial: 15 percent of 8th graders reported heavy drinking, as did 24 percent of 10th graders, 28 percent of 12th graders, and 34 percent of college students.

High school seniors reported a decrease in monthly prevalence of alcohol use from 72 percent in 1980 to 50.1 percent in 1994 (Johnston et al. 1995). Daily use decreased from 6.9 percent in 1979 to 2.9 percent in 1994, as did the prevalence of consuming five or more drinks in a row during the prior 2 weeks, from 41 percent in 1983 to 28 percent in 1994 (Johnston et al. 1995). It should be noted, however, that a 1993 change in the wording of the questionnaire may have contributed to the most recent reported decreases in alcohol use among high school seniors. Nevertheless the rates, though decreased, remain a concern.

Monthly prevalence of alcohol use for college students showed less decline (from 82 percent in 1980 to 67.5 percent in 1994), and less decrease was observed in daily use (from 6.5 percent in 1980 to 3.6 percent in 1994) (Johnston et al. 1996). The rate of daily use reported by college students in most surveys since 1980 was slightly lower than that of their noncollege peers, although this was not true in 1994. The noncollege group experienced a considerable drop in the rate of daily drinking between 1981 (8.7 percent) and 1994 (3.2 percent) (Johnston et al. 1996).

. . . although purchase of alcohol is illegal for all high school students and most undergraduate college students, most have had experience with alcohol.

The findings for college students are quite high, especially in light of data showing that high school seniors and peers not in college had a net decrease in heavy drinking since 1980. Furthermore, because college-bound seniors in high school are less likely than non-college-bound seniors to report heavy drinking, these findings may indicate college students' "catching up" and possibly surpassing their contemporaries who do not attend college.

Among college students, the pattern of binge drinking is widespread. In 1994, 40 percent of college students reported binge drinking (defined as drinking five or more drinks at one sitting) at least once within 2 weeks of being surveyed (Johnston et al. 1996). The prevalence of binge drinking varies between genders, with 31 percent of college women and 52 percent of college men reporting such drinking in 1994 (Johnston et al. 1996). Among college campuses, the prevalence also varies, ranging from 0 to nearly 70 percent of the students (Wechsler et al. 1994). Rates appear to differ depending on the type of college, its geographic location, and the ethnic and gender makeup of the student body (Presley et al. 1995; Wechsler et al. 1994).

Analyses also have been conducted using the National Longitudinal Survey (NLS) of Labor Market Experience in Youth, which began in 1979 with a representative sample of 14- to 21-year-olds to investigate how youth enter the labor market. In this ongoing survey, respondents are interviewed every year and are asked about their alcohol use. Harford's (1993) analysis, which used data from 1982, 1984, and 1988, found that about 87 percent of the men and 58 percent of the women maintained their drinking status throughout the 6-year segment of the study: 71 to 73 percent of those interviewed were current drinkers (used *any* amount of alcohol in any frequency during the previous month) at all three points of the study, approximately 30 percent were heavier drinkers (six or more drinks per occasion at least two to three times in the previous month), and 6 percent reported abstaining from alcohol use. A large increase in current and heavier drinking between the ages of 17 and 18 was reported; however, both current drinking and heavier drinking decreased with increasing age.

Cook and Moore (1993) used the two youngest cohorts and the high school subsample of the NLS data to assess the effect of drinking on years of schooling and the likelihood of college graduation. They found that heavy drinking in high school was associated with a reduction in the average number of years of education beyond high school. Furthermore, they reported that high school students who resided in States with relatively high taxes and a high minimum drinking age were more likely to graduate from college.

Trend data from the 1984 and the 1990 NASs also provide information on youth, alcohol use, and alcohol-related problems. A significant decrease in weekly drinking was found for respondents 18 to 29 years old (from 40.1 to 32.2 percent); however, the gender-specific differences were not significant for this age group (table 3). Similarly, although rates of current drinking decreased for men and women and rates of heavier drinking decreased primarily for men, these changes were not significant.

In contrast to decreases in specific drinking patterns, there was a significant increase (from 16.9 to 25.9 percent) (table 7) in reports of two or more social consequences for the 18- to 29-year-old group between 1984 and 1990 (Midanik and Clark 1995). This age group also had the highest proportion of individuals reporting both dependence symptoms and social consequences, which is consistent with other national surveys (Clark and Hilton 1991). Moreover, the 18- to 29-year-olds had the highest proportion of individuals classified as alcohol abusers and alcohol dependent (Caetano and Room 1994; Caetano and Tam 1995; Grant et al. 1994). For example, Grant et al. (1994) found that 15.94 percent of younger respondents reported symptoms of alcohol abuse or dependence compared with 7.41 percent in the overall population (table 9).

Older Adults

Because studies of people who are at least 65 years old consistently show that they drink less alcohol and report fewer alcohol-related consequences, alcohol abuse, or dependence compared with younger persons, relatively few epidemiologic studies have focused specifically on older adults. However, age-group comparisons of drinking patterns based on cross-sectional and trend data derived from national surveys can provide information on how drinking patterns and reports of problems may have shifted within this older group.

Data from both the 1984 and the 1990 NAS (table 3) reveal a lower proportion of current drinkers, weekly drinkers, and heavier drinkers (five or more drinks on one occasion at least weekly) among individuals 60 years of age or older than among the four other age groups. From 1984 to 1990, the proportion of current drinkers decreased from 48.9 to 37.0 percent among women 60 years of age and older; among men in the same age group, there was no significant change from 1984 to 1990. There were also no significant changes in either gender in the proportion of those 60 years old and older who reported weekly drinking or heavier drinking during the last year (Midanik and Clark 1994).

Similar to the data on drinking patterns, respondents 60 years of age and older had the lowest proportion reporting three or more dependence symptoms or two or more social consequences compared with younger respondents. Also, no significant changes were found for either dependence symptoms or social consequences (Midanik and Clark 1995).

Rates of alcohol abuse and dependence are also consistently lower in the older age group than in the other age groups. Grant et al. (1994) found in the NLAES data set that the overall percentage of alcohol abuse and dependence (as defined by DSM-IV) for individuals 65 years of age and older was 0.64, which was very low compared with the percentage for adults 18 to 29 years old (15.94 percent), 30 to 44 years old (7.27 percent), and 45 to 64 years old (3.47 percent). However, the rates of alcohol abuse and dependence varied by gender and race for this older group. Older nonblack men had the highest percent of alcohol abuse and dependence (1.21 percent), followed by all men (1.18 percent), black men (0.82 percent), nonblack women (0.29 percent), and all women (0.27 percent). Alcohol abuse or dependence was not found in older black women. This general relationship between age and alcohol abuse and dependence (or alcohol dependence only) has been reported in other studies (Caetano and Room 1994; Grant et al. 1992).

In an extensive review of alcohol use and alcoholism in older persons, Liberto et al. (1992) assessed 21 cross-sectional studies conducted between 1960 and 1990 and 8 studies of hospital and outpatient samples of older persons during the same period; most patients in these studies were at least 60 years of age. The following findings were consistent in cross-sectional studies: There is less use of alcohol in older populations than in middle-aged populations; the prevalence of abstainers is highest in the older population; the prevalence of heavy drinking and alcohol abuse is lower in this population than in younger populations; and older men drink more frequently and in greater quantities than older women. From the longitudinal studies reviewed, Liberto et al. concluded that alcohol use is fairly constant (or may decrease slightly) over time among older light drinkers; the prevalence of abstention is higher with increasing age; heavy drinking declines with increasing age; and men drink more frequently and in greater quantities than women.

As the population continues to age, assessment of drinking patterns and consequences of alcohol use among older persons will become increasingly important (Dufour and Fuller 1995). Lower rates of alcohol use and fewer reports of alcohol-related problems in the elderly than in younger age groups can no longer preclude the design and implementation of epidemiologic (and other) studies of alcohol use and abuse among the elderly in this country. Further investigation should focus not only on quantity-frequency measures for this age group but also on the physical and health characteristics unique to older persons as well as the interaction between these characteristics and alcohol use and abuse. Specific examples include the influence of alcohol intake on over-the-counter and prescription drug use (and vice versa) among older persons and the effect of lower alcohol intake levels on medical and other consequences, compared with effects of the same consumption levels in younger persons.

Ethnic Minorities

Differences in alcohol use and alcohol-related problems within and across ethnic minorities have become increasingly important as the proportion of ethnic minorities in the population has increased. Unfortunately, many national epidemiologic studies aimed at describing drinking patterns and associated problems consist of sample sizes that do not enable valid comparisons across ethnic groups, and analyses involving collapsed ethnic categories make it difficult to disentangle the effects of ethnicity from other effects. Moreover, within ethnic groups, there is often an assumption of homogeneity that does not reflect actual differences in drinking patterns associated with different subgroups of a more broadly defined ethnic group (e.g., the Hispanic group includes persons of Mexican, Cuban, and Puerto Rican heritage). Despite this issue, descriptive information can be obtained and, in some cases, corroborated by other studies.

Differences in alcohol use and alcohol-related problems within and across ethnic minorities have become increasingly important as the proportion of ethnic minorities in the population has increased.

In the 1984 and 1990 NASs (table 3), the overall decrease in the proportion of current drinkers, weekly drinkers, and heavier drinkers was significant *only* for white respondents (Midanik and Clark 1994). Although not statistically significant, the rate of heavier drinking among Hispanic respondents also increased. This cross-sectional finding is corroborated by Caetano and Kaskutas' (in press) analysis of the results of a 6-year followup of white, black, and Hispanic respondents from the 1984 NAS. The authors found heavy drinking decreased only among white men (from 19 to 12 percent). The change in the proportion of heavy drinkers from 1984 to 1990 for both the black and the Hispanic respondents was less marked. When alcohol-related problems such as social consequences and dependence symptoms were examined in the 1984 and 1990 NASs (Midanik and Clark 1995; table 7), no significant differences were found in reports of either type of problem for any ethnic group. The rates of reports of both three or more dependence symptoms and two or more social consequences were relatively stable for white respondents. Among black and Hispanic respondents, where sample sizes were small, rate increases for dependence symptoms and social consequences were observed (sometimes increases that appear quite substantial), but they were not statistically significant. It has been suggested that the greater stability of heavy drinking among blacks and Hispanics helps to explain higher rates of problems reported in the literature for these two groups and that prevention efforts targeting these two groups should be intensified (Caetano and Kaskutas 1995).

Additional research has been conducted on drinking problems and drinking contexts among black and white men and women by using the 1984 NAS, which oversampled black and Hispanic respondents. Herd and Grube (1993) compared the social settings of drinking for black and white women and also determined whether drinking in different settings has an independent effect in predicting alcohol-related problems. Compared with black women, white women were more likely to attend restaurants, bars, and parties away from home; furthermore, a larger proportion of alcohol use among white women than black women occurs in settings outside the home. The authors also found that drinking contexts independently predicted drinking problems and that race was not directly associated with drinking contexts or alcohol-related problems. In other words, the relationships between race, frequency of drinking in different social contexts, and reports of alcohol-related problems are indirect and complex.

Using the same data set, Herd (1994) examined predictors of drinking problems among black and white men. She found that although black men reported higher mean scores for many different alcohol-related problems, they did not report higher rates of heavier drinking or drunkenness, nor did they have significantly higher mean scores on a scale rating permissiveness of drinking norms. She also found that race independently predicts alcohol-related problems even when social and demographic variables are controlled for and that race interacts significantly with frequency of heavier drinking and some sociodemographic characteristics. As the frequency of heavier drinking increases, rates of drinking problems rise at a more rapid rate among black men than among white men.

Using data from a collaborative study between Japan and the United States, Parrish et al. (1992) assessed the relationship of drinking levels (average alcohol use) and drinking attitudes ("appropriate" alcohol use in specific situations) among three groups. Data were collected through interviews in 1984 and 1985 of Japanese men and women residing in Japan, Hawaii, and California. Results indicated that drinking attitudes differed significantly among drinking levels (abstaining, light, moderate, heavy) and that drinking levels were good predictors of drinking attitudes within samples. Among men, increased alcohol consumption was associated with more tolerant drinking attitudes for most situations. This finding was not as strong for men in Japan, as for Japanese-American men, and the association was weakest among Japanese women. Similarly, Higuchi et al. (1994) found much higher average consumption rates among Japanese men than among Japanese-American men at all ages, suggesting a moderation in drinking patterns among men of Japanese descent as a consequence of acculturation.

The relationships between race, frequency of drinking in different social contexts, and reports of alcohol-related problems are indirect and complex.

In examining alcohol use among American Indians, Dick et al. (1993) assessed patterns and correlates of alcohol use of American Indian adolescents (grades 9 through 12) in a boarding school (N = 188). Approximately 86 percent of the sample had tried alcohol at some time. Data revealed a statistically significant association between strong family support and lower self-reported rates of alcohol use and intoxication. Stressful life events and emotional distress were associated with an increase in drinking, and peer pressure was not related to alcohol use in this sample. Dick et al. (1993) note that lack of longitudinal data prohibits better understanding of the long-term effects of these relationships on individual patterns of alcohol use among American Indians.

Walker et al. (1994) assessed the demographic, clinical, and treatment episode characteristics of 3,087 American Indian veterans discharged from Veterans Administration hospitals in 1991. Substance use disorders were diagnosed in 46.3 percent of American Indian veterans and 23.5 percent of all discharged veterans. Among those American Indians with substance use disorders, 97 percent had a diagnosis of alcohol dependence. American Indians who were substance dependent were more likely than non-substance-dependent American Indians to be younger, male, and unmarried and to also have psychiatric disorders, such as personality disorders, depression, and posttraumatic stress disorders. Rehospitalization rates were also higher among substance-dependent American Indian veterans than among those who were not substance dependent.

Leung et al. (1993) conducted a community study of an American Indian village to examine the natural history of alcoholism over 19 years (1969–1988). Evaluation of data from this study revealed that the prevalence rate of alcoholism was high but had decreased over the 19-year period (from 39 to 21 percent). Using three different methods, the authors assessed remission rates within this population: All three methods yielded approximately 60 percent. The first method, which calculated remission rates by the life history method, found an overall rate of 63 percent (52 percent for men and 82 percent for women). (This rate is higher than rates from the Epidemiologic Catchment Area studies, which found an overall rate of 51 percent [50 percent for men and 53 percent for women].) The second method calculated remission rates from a group of 30 alcoholics followed for the 19 years; it showed that 10 had no current alcohol diagnosis, 8 died of non-alcohol-related causes, 8 had a current alcohol diagnosis, and 4 had died of an alcohol-related disorder, yielding an overall remission rate of 60 percent (i.e., 18 out of 30). The third method followed a cohort of the population to determine the remission rate for all those who developed alcoholism; this rate was 60.9 percent.

Most people in the village who stopped drinking did so spontaneously or for specific personal reasons rather than as a response to specific alcohol treatment. However, caution must be used in extrapolating these results to other groups or to the general population because the results were derived from a small sample and from a particular culture. Leung et al. (1993) speculated that a combination of economic, social, and cultural processes may be responsible for strong tribal identity and stability, which are not found outside this specific culture but may affect the ways in which alcohol is used in this particular tribe.

Summary

Per capita alcohol consumption began to decline in the 1980s, and the trend continued through 1993, when the per capita consumption level dropped to 2.25 gallons of alcohol. This per capita consumption level represents the lowest level recorded since 1964. Decreases in per capita consumption have been accompanied by increases in overall abstention rates and decreases in rates of heavier drinking and other drinking patterns, such as weekly drinking. Several factors may have contributed to the decrease in per capita consumption in the United States, including less tolerant national attitudes toward drinking, increased societal and legal pressures and actions against drinking and driving, and increased health concerns in Americans.

Despite the declines in per capita alcohol consumption, alcohol-related morbidity and mortality remain significant problems in this country. For example, estimates suggest that as many as 45 percent of the 45,000 traffic crash fatalities each year involve alcohol. Alcohol-related traffic crash fatalities, however, are decreasing: In 1993, 14,255 people died in alcohol-related traffic crashes, which is the lowest number recorded in the last 17 years. Young drivers continue to be overrepresented in drinking driver deaths. In 1993, persons aged 16 to 24 accounted for 28 percent of all drinking driver deaths; however, they represented only 15 percent of all licensed drivers in the United States. Male drivers also are more frequently involved in fatal traffic crashes than are female drivers, and approximately twice as many male drivers had been drinking.

International data indicate that alcoholic cirrhosis is found in all countries. In the United States, cirrhosis accounted for 25,407 deaths in 1992, making it the 11th-leading cause of death. Although cirrhosis remains a substantial problem, mortality rates have been declining in this country since 1970 except among persons aged 75 and older. Researchers have proposed various reasons that may account for the decline in cirrhosis mortality, including increases or changes in treatment for alcohol problems and improvements in prevention and nutrition.

In 1993, alcohol-related diagnosis was listed first in the medical records of about 429,000, or 1.5 percent, of short-stay hospital discharge episodes. This percentage has remained somewhat stable since 1979, whereas the percentage of hospital discharges with any mention of alcohol-related diagnoses has increased. How much of this increase is real and how much of it may be due to a greater awareness of alcohol-related problems by health care professionals is unclear. Hospital discharge records, however, may actually underrepresent the prevalence of alcohol use disorders among hospitalized patients. This idea is supported by a study that found that 22 percent of patients screened positive for alcohol problems on admission to the hospital, whereas only 7.4 percent of the patients had an alcohol-related diagnosis on their discharge records.

In addition to health problems, abusive drinking can lead to legal, social, and job-related problems. According to survey data, there have been no overall changes in reports of social consequences or dependence symptoms among current drinkers in the general population despite decreases in alcohol consumption, specific drinking patterns, and liver cirrhosis mortality. However, among young persons, individuals who have never married, and those not employed, reports of two or more social consequences increased significantly between 1984 and 1990. In addition, reports of three or more dependence symptoms increased among unemployed respondents between 1984 and 1990. Using risk-function analysis, U.S. and Canadian data show some degree of risk for harm even at lower levels of drinking, suggesting that there is no clear lower threshold of drinking at which an individual can be "completely safe" from experiencing some consequences.

Data from a large 1992 U.S. household probability sample indicated that approximately 7.4 percent, representing 13,760,000 Americans, could be classified as having alcohol abuse, alcohol dependence, or both in the past year. Prevalence rates of alcohol abuse and dependence are higher for men than women and for younger respondents than older respondents.

Studies confirm that women drink less and report fewer alcohol-related problems than men do. Rates of abstention among women have been rather stable, but rates of heavy drinking among women have declined during the past 10 years. Paradoxically, women, specifically younger women, have reported higher rates of intoxication despite lower rates of heavy drinking; these data suggest a cultural or cohort effect related to how women perceive the effects of alcohol use. No empirical evidence supports the claims that women's drinking is approaching that of men; that is, the convergence hypothesis. Future studies focusing on women and alcohol use should take into account special factors such as childhood and adult violent victimization, depression, sexual experience, and the influence of husbands' or partners' drinking.

Although alcohol use among youth has historically been greater than use of illicit drugs, survey data have found that rates of monthly and daily alcohol use among high school seniors, as well as the proportion of youth who drank heavily (i.e., five or more drinks in a row in the last 2 weeks), continue to decrease. Despite this decrease, alcohol use among high school and college students remains a concern.

Compared with non-college-bound youth, college students have shown less of a decline in monthly and daily use prevalence rates and little change in the proportion of heavy-drinking students. Binge drinking (defined as drinking five or more drinks at one sitting) among college students has become a widespread problem. Data suggest that this pattern of drinking varies between genders and among college campuses.

Consistent findings from epidemiologic surveys on alcohol use show that older adults—particularly those over 60 years old—have a higher proportion of abstainers and a lower proportion of heavy drinking and alcohol abuse than younger age groups have. Rates of alcohol dependence, in addition to being stable, are lower in this age group than in other age groups. Older men drink more frequently and in greater quantities than older women. Lighter drinking patterns remain stable with older age, but heavier drinking patterns tend to decrease with aging. Older nonblack men have the highest rates of alcohol abuse and dependence.

Research has identified variations in rates of alcohol use and alcohol-related problems for different ethnic groups. Although overall decreases and, more recently, stabilization in alcohol use have been observed in the U.S. population, these changes are not necessarily representative of broadly defined ethnic groups, such as blacks and Hispanics, or of more narrowly defined ethnic or cultural groups, such as specific American Indian tribes. For example, reports of social consequences of alcohol use and abuse suggest that within specific ethnic groups, rates may not be stable and, in fact, may be increasing. By recognizing that differences exist between the total population and certain subgroups, researchers have begun to lay a foundation for identifying these differences and tailoring future studies to maximize the potential for intervention and prevention strategies and programs targeted at growing ethnic minority groups.

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Chapter 2

Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse

Introduction

Although the determinants of drinking behavior are diverse and complex, researchers have been successful in identifying the fundamental components that influence alcohol use and abuse in humans. Scientists have established, for example, that alcoholism runs in families and that genetic factors contribute substantially to a familial vulnerability for the disease. Building on this finding, geneticists now are working toward discovering the specific genes that contribute to risk for alcoholism; determining whether and how the transmission of alcoholism in families is moderated by gender and other factors; and identifying the neurophysiologic, biological, and psychological factors that influence the relationship between primary gene products (protein synthesis) and drinking behavior.

Researchers have been particularly productive in identifying the individual heritable characteristics that predict risk for alcoholism. Scientific evidence indicates that, on average, those who are at high risk for developing alcoholism by virtue of their family history differ biochemically and neurophysiologically from those who are at low risk. Reactions to alcohol and certain critical personality characteristics also appear to distinguish groups of high- and low-risk people.

Studies have revealed, however, that individual differences in drinking behavior cannot be accounted for by genetic and biological factors alone. Psychologists have identified basic cognitive processes that influence drinking behavior and have shown how those processes might temper the effects of biological factors. Social scientists have determined how family, peer, and social context can influence drinking attitudes and behaviors, and anthropologists have investigated the role that culture plays in determining who drinks, when they drink, and how much they drink. Thus, the risk for alcoholism is determined by a complex interplay of genetic, psychological, and environmental factors.

In recent years, researchers in the alcohol field have begun to test and apply integrative models that simultaneously consider the multiple biological, psychological, and sociocultural factors that can influence drinking behavior. These models emphasize the gradual process by which contextual factors can transform heritable characteristics to either promote or impede the expression of alcohol problems. The models also explore the reciprocal influence that biological and nonbiological factors can impose over time. Notably, alcohol researchers have begun to move away from an arbitrary dichotomy that implicitly pits the biological against the nonbiological and toward conceptual orientations that emphasize the interplay between these two types of factors.

Accordingly, this chapter discusses recent findings about the multiple components that influence drinking behavior. The specific topics addressed range from family and genetic influences to developmental models.

The sequential organization of the chapter allows findings for each topic to be presented separately. These factors, however, are not independent of one another. They may interact to influence drinking behavior, or they may be measures of similar processes at different levels of biopsychosocial organization.

Family and Genetic Influences

A positive family history for alcoholism is one of the most consistent and powerful predictors of a person's risk for developing the disease. Research has convincingly demonstrated that alcoholism runs in families. First-degree relatives of alcoholics are two to seven times more likely than the general population to develop problems with alcohol sometime in their lifetime (Cotton 1979; Merikangas 1990). A family history of alcoholism, however, subsumes the influences of genetic factors and a shared family environment. Consequently, the observation that alcoholism runs in families, although important, does not by itself unequivocally define the mechanisms that underlie that familial association. A principal focus of current alcoholism research is to identify and characterize the processes by which a predisposition for alcoholism is transmitted in families.

> *A positive family history for alcoholism is one of the most consistent and powerful predictors of a person's risk for developing the disease.*

Genetic and Environmental Influences on Familial Transmission

Unlike family studies, twin and adoption studies offer researchers the opportunity to examine the independent contributions of genetics and environment to alcoholism. (The sixth, seventh, and eighth volumes of the *Special Report to the U.S. Congress on Alcohol and Health* include detailed discussions of the methods and findings of twin and adoption studies.) Findings from such studies have demonstrated that genetic determinants play an integral role in a person's increased risk for developing the disorder (McGue 1994). Twin studies of alcoholism have revealed a greater concordance[1] for the disease among identical twins, who are genetically identical, than among fraternal twins, who are no more genetically alike than nontwin siblings (Cadoret 1990; Kendler et al. 1992; McGue et al. 1992; Pickens et al. 1991). Adoption studies have shown that the biological offspring of alcoholics possess a heightened risk for alcohol abuse even when they are adopted away and reared by nonrelatives (Bohman et al. 1981; Cloninger et al. 1981; Goodwin et al. 1973; Sigvardsson et al. 1996).

Although it is clear that genetic factors influence risk for alcoholism, these factors alone cannot account for individual differences in drinking behavior. Adoption and twin studies indicate that psychological, developmental, and environmental determinants also contribute to heightened risk for alcoholism. Research findings suggest that children of alcoholics are at increased risk for developing alcoholism and related behavioral disorders not only because of the influence of genetic factors but also because they are more likely than children of nonalcoholics to grow up in families that are marked by relatively high levels of marital discord (McLeod 1993) and parental hostility (Johnson and Pandina 1991); relatively low levels of parental monitoring (Peterson et al. 1994) and parental warmth (Johnson and Pandina 1991); and relatively high levels of parental tolerance of adolescent drinking (Webster et al. 1994). In many cases, the expression of a behavioral dysfunction, such as alcoholism, in the offspring of alcoholics may arise because a disordered rearing environment can potentiate an inherited vulnerability to the disease (Cloninger 1987).

Children of alcoholics are more likely than children of nonalcoholics to abuse alcohol and other drugs during adolescence (Chassin et al. 1991; Pandina and Johnson 1990). The increased risk of adolescent alcohol and other drug problems observed among the children of alcoholics reflects a relatively early initiation and rapid escalation of their substance use (Chassin and Barrera 1993; Labouvie et al. 1991). Children of alcoholics also have a greater vulnerability for certain psychopathologies than do children of nonalcoholics (West and Prinz 1987). Reich et al. (1993) reported that the preadolescent and adolescent offspring of alcoholics were significantly more likely than the offspring of nonalcoholics to be diagnosed with oppositional disorder or conduct disorder or as overanxious. The adolescents with alcoholic parents were not significantly more likely, however, to meet criteria for either clinical depression or attention-deficit disorder.

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[1] Concordance rates indicate the extent to which a trait is found in both members of a twin pair.

In an effort to more fully understand the etiology of alcohol problems, researchers continue to focus attention on identifying the specific environmental factors and developmental processes that interact with genetic determinants to increase a person's vulnerability for developing alcoholism. In addition, they are exploring the nature of the relationship among these three factors to try to assess how much each contributes to predisposition for the disease. Characterizing the multifactorial and developmental nature of inherited risk should lead to a better understanding of how genetic factors are modulated by familial environmental and sociocultural influences. This knowledge should help to identify critical periods in the development of alcohol use disorders. As well, this knowledge can have considerable implications for the prevention of alcohol problems, early detection and intervention for individuals who are at risk, and design of effective treatments for alcoholism.

Resilient Offspring of Alcoholics

Most people reared in an alcoholic home never develop an alcohol problem or manifest an alcohol-related behavioral disorder (Ohannessian and Hesselbrock 1993). In light of this, researchers have questioned whether there are factors that protect or render some individuals resilient to alcoholism, even though they are at high risk for the disease because of family history. Identifying the factors that contribute to such a behavioral resilience can be important to the design of prevention approaches.

Evidence suggests that family functioning and social support may moderate the negative effect of parental alcoholism. According to one study (Barnes et al. 1995), high levels of parental support, close monitoring of adolescent activity by parents, and positive adolescent-parent communication could all serve to modify the effects of parental alcohol abuse on adolescent alcohol use. Among adults with a family history of alcoholism, Ohannessian and Hesselbrock (1993) observed increased rates of alcohol abuse only for those who perceived that they had low social support from friends. The investigators found, however, that perceived support from family members did not provide a protective effect, suggesting that the source of social support may be an important factor in moderating the effect of a positive family history.

Observing abusive drinking in a parent may help to protect against the development of drinking problems in some offspring. In a study by Harburg et al. (1990), 63 percent of the children of problem-drinking fathers were either light drinkers or abstemious compared with 48 percent of the children of non-problem-drinking fathers. (The number of problem-drinking mothers in the study was too small to examine reliably the effects of maternal alcohol abuse.) The researchers suggested that the children with problem-drinking fathers had developed an aversion to drinking after witnessing the consequences of abusive alcohol use on a loved one. The timespan of a parent's drinking problem also may affect the development of drinking problems in offspring. In a longitudinal study of adolescent substance use, Chassin and Barrera (1993) reported a more rapid escalation of alcohol use among the offspring of alcoholic fathers who had continuous alcohol-related problems throughout the course of the study than among both the offspring of nonalcoholic fathers and the offspring of alcoholic fathers who did not have continuous problems from drinking.

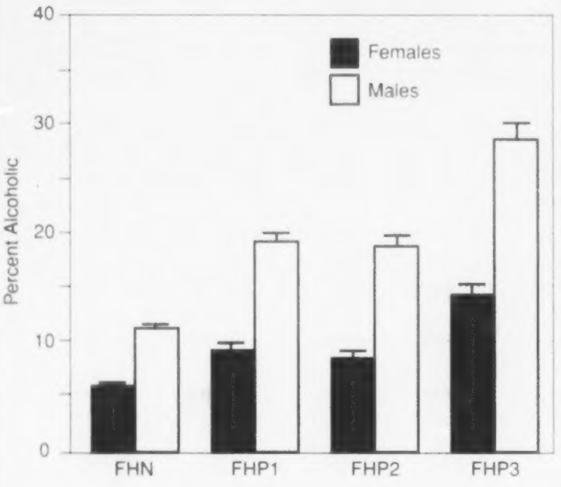
The frequency of alcoholism in a family, or the degree of family loading, may influence a person's risk for developing the disease. In a survey of more than 20,000 adult drinkers, Dawson et al. (1992) observed that the risk for alcohol dependence varied for different categories of affected relatives. Compared with the odds of alcohol dependence among individuals with a negative family history of problem drinking, the odds of alcohol dependence were 45 percent greater among individuals with a problem-drinking second- or third-degree relative only, 86 percent greater among individuals with a problem-drinking first-degree relative only, and 167 percent greater among individuals with at least one problem-drinking first-degree relative and at least one problem-drinking second- or third-degree relative (figure 1). The extent to which this increased risk for problem drinking results from genetic factors, environmental factors, or some combination of the two remains to be determined.

Inheritance of Alcoholism in Women

Most of the early behavioral genetic studies in alcoholism included study samples composed primarily of men and generated findings that addressed the heritability of alcohol problems in this population only. Recent years, however, have seen an increased interest in identifying the influence of inherited factors on alcoholism in women. Family studies of alcoholism have

Figure 1. Rate of alcoholism as a function of family history.

Figure gives the percentage of current drinkers meeting DSM-III-R criteria for alcohol dependence as a function of their family background. Rates are based on the reports of 23,152 drinkers aged 18 years and older. FHN = no family history of alcoholism. FHP1 = family history of alcoholism in second- or third-degree relatives only. FHP2 = family history of alcoholism in first-degree relatives only. FHP3 = family history of alcoholism in first-degree relatives and either second-degree or third-degree relatives.



Source: Dawson et al. 1992. Reprinted by permission. Dawson, D.A.; Harford, T.C.; and Grant, B.F. Family history as a predictor of alcohol dependence. *Alcoholism: Clinical and Experimental Research* 16(3):572–575, 1992.

indicated that the female relatives of alcoholics, like their male counterparts, are at increased risk for developing alcoholism (Pollock et al. 1987). Initial twin and adoption research on female alcoholism, however, suggested that genetic factors contributed minimally, if at all, to the inheritance of alcoholism in women (McGue and Slutske in press). Of note is that the relatively small samples of female alcoholics included in these early studies precluded any unequivocal conclusions about the existence of gender differences in the heritability of alcoholism.

A recent large twin-family study has provided the strongest evidence yet published on the influence of genetic factors on the expression of alcoholism in women. Kendler et al. (1994) studied 1,030 adult female twins and 1,468 of their parents. A diagnosis of alcoholism in the study was based on standard diagnostic criteria for alcohol dependence as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)* (American Psychiatric Association 1987). The investigators reported that the rate of alcoholism among the co-twins[2] of affected identical twins (31.6 percent) significantly exceeded the corresponding rate among the co-twins of affected fraternal twins (24.4 percent). Moreover, the rate of alcoholism among both identical and fraternal twins exceeded the rate observed among the daughters of alcoholic mothers (15.6 percent) and the daughters of alcoholic fathers (14.1 percent) (figure 2). In an analysis of the combined twin-family data, Kendler et al. (1994) estimated that the heritability of alcoholism liability ranged from 51 to 59 percent, with the balance of variance (41 to 49 percent) being attributed to environmental factors not shared by these adult twins who were reared together.[3] According to this study, genetic influences account for approximately 50 percent of alcoholism in women, an estimate similar to that reported in studies of male alcoholic twins (McGue 1994).

Although the study by Kendler et al. (1994) indicates that genetic factors contribute to the risk for alcoholism in women, it also demonstrates that such factors do not account entirely for expression of the disorder. Among the pairs of identical twins studied, nearly 70 percent of the co-twins of alcoholic women did not meet criteria for alcoholism. Even when a broad definition of alcohol abuse was used (i.e., one that yielded a positive diagnosis when as few as one symptom was included), alcoholism was diagnosed in only one twin of an identical pair in more than 50 percent of the cases examined. As any difference between the two members of a genetically identical twin pair must be environmental in origin, this finding indicates that environmental factors must play a substantial role in the etiology of alcoholism in women, as is true for men.

Molecular Genetic Research

Twin and adoption studies have demonstrated that one or more of the estimated 50,000 to 100,000 genes that compose the human genome influence risk for alcoholism. Alcoholism is considered to be a polygenic

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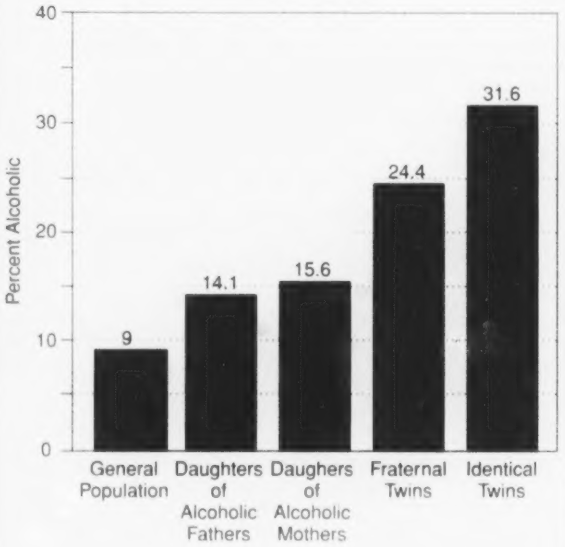
[2] A co-twin is one member of a pair of twins.

[3] In studying liability, researchers try to estimate the contribution of genetic and environmental effects to a person's liability for alcoholism. Liability may be thought of as the outcome of genetic and environmental risk factors that together produce a person's total risk for developing alcoholism (Falconer 1965).

Figure 2. Rate of alcoholism in women among female relatives of an alcoholic.

Figure gives the prevalence of DSM-III-R alcohol dependence for female participants in a twin-family study of alcoholism according to alcoholism status of their relatives. Rates are given for a lifetime diagnosis of alcohol dependence and are based on findings from a study of 1,030 female adult twin pairs and 1,468 of their parents.



Source: Kendler et al. 1994. *American Journal of Psychiatry* 151(5):707–715, 1994. Copyright 1994, the American Psychiatric Association. Reprinted by permission.

disorder, influenced by many genes located in different areas, or loci, of a person's DNA (Goldman 1993; McClearn et al. 1991). Positional cloning, a group of techniques that allow disease genes to be identified solely on the basis of their location within a person's total genetic material (i.e., genome), is the primary strategy now used by molecular geneticists to identify the specific genes involved in a human disorder such as alcoholism. Once genes are identified, they can be cloned for study. Until recently, however, the feasibility of the positional cloning strategy was severely limited by the small number of known genetic markers (Lander and Schork 1994). Genetic markers are inherited characteristics—for example, differences in DNA segments or in protein molecules—that occur with a disease, such as alcoholism, more frequently than chance would indicate. A marker, which is known to occupy a particular place on a chromosome, can be a gene or may be derived from a region of the genome that does not produce a functional product. If a marker gene is located on the chromosome and in proximity to the gene or genes responsible for a particular disease, then the marker and the disease genes are considered to be linked.

The prospects for positional cloning with human disease changed dramatically with the recognition by Botstein et al. (1980) that variations in DNA, or DNA polymorphisms, provide a rich and nearly limitless source of genetic marker information. Each marker is polymorphic; that is, it exists in several different variants that can distinguish individuals from one another (Grisel and Crabbe 1995). In a relatively short period of time, the discovery of DNA polymorphisms has led to the construction of a comprehensive human linkage map (Murray et al. 1994); the genetic mapping of more than 400 human disorders caused by a single defect in a single gene (i.e., Mendelian disorders); and the prospect of identifying the genes influencing the expression of complex human disorders (i.e., non-Mendelian disorders), such as hypertension, diabetes, schizophrenia, manic-depressive disorder, and alcoholism (Lander and Schork 1994). Complex human disorders are caused by the effects of several genes interacting with the environment.

Positional cloning begins with identifying the chromosomal region that includes a disease-susceptibility gene and ends with precisely localizing and cloning the relevant DNA sequence for the disease. As is the case with research on other complex traits, attempts to localize genes involved in the etiology of alcoholism are primarily at the initial stage of this process; that is, identifying the relevant chromosomal regions.

Two methods, namely association techniques and linkage approaches, are used currently to localize a gene to a specific region of a chromosome. An association study seeks to determine whether there is a statistical association between a genetic marker and disease status at the population level. A linkage study seeks to determine whether there is an association between a genetic marker and disease status within families (i.e., whether gene marker and disease status cosegregate within families). Application of these methodologies in alcohol research has involved primarily two systems, the dopamine D_2 receptor locus (DRD_2) and polymorphisms affecting alcohol metabolism.

The DRD_2 Locus and Alcoholism

Experimental evidence from studies of nonhuman mammals has suggested that the dopaminergic system in the brain is involved in the voluntary consumption of alcohol (Wise and Rompre 1989). Accordingly, polymorphisms that influence dopamine neurotransmission constitute candidates for genes that may influence the etiology of human alcoholism.

Blum et al. (1990) first reported an increased prevalence of the A1 allele[a] of the human dopamine DRD$_2$ receptor gene (located on chromosome 11) and hypothesized that the A1 allele may be a marker for heightened responsiveness to pharmacologic stimulation and a somewhat abnormal DRD$_2$ receptor function in the brain reward system. DRD$_2$ receptors function in the psychomotor activation system pathways of the brain, and their drug-induced stimulation appears to be rewarding (Wise 1988). The investigators noted that 24 (69 percent) of the 35 alcoholics examined carried at least one copy of the A1 allele compared with only 7 (20 percent) of the nonalcoholics studied. Given the potential significance of this finding, several laboratories quickly tried to replicate a DRD$_2$ association with alcoholism. These early reports yielded both positive and negative evidence about the association (Uhl et al. 1993).

Two methods, namely association techniques and linkage approaches, are used currently to localize a gene to a specific region of a chromosome.

As additional studies on the association of DRD$_2$ markers with alcoholism have been published, however, the statistical evidence supporting an association has eroded. Gelernter et al. (1993) concluded in a review that a statistical association between DRD$_2$ and alcoholism was not supported when all relevant studies were considered. Aggregating across all published reports, the frequency of the A1 allele was 0.21 among 502 alcoholics, 0.20 among 307 control individuals not screened for alcoholism, and 0.12 among 186 control individuals screened for alcoholism. Moreover, in a study of 113 alcoholics and 34 controls, Gejman et al. (1994) failed to identify any sequence mutation in the DRD$_2$ gene in association with alcoholism that would alter the function of the D$_2$ receptor. Suarez et al. (1994) concluded that it was unlikely that the A1 site at DRD$_2$ was physically proximal to a functional mutation in another gene affecting risk of alcoholism. In the absence of both strong statistical support for an association and identification of functional differences in the DRD$_2$ gene associated with alcoholism, there is no compelling evidence at this time that polymorphisms at DRD$_2$ exert a significant influence on alcoholism risk.

The failure to unequivocally establish an association between alcoholism and DRD$_2$ has been disappointing yet illuminating. The debate surrounding research on DRD$_2$ has helped to identify many of the issues that need to be addressed in the design of future molecular genetic research on alcoholism. First, it is clear that in future association studies, alcoholic and control groups must be carefully matched on ethnicity. The frequency of the A1 allele at DRD$_2$ has been shown to vary more than eightfold across various ethnic groups, being relatively low among certain Middle Eastern populations, intermediate among Caucasians, and relatively high among certain North American Indian populations (Barr and Kidd 1993; Goldman et al. 1993). Because the frequency of alcoholism also varies with ethnicity (Helzer and Canino 1992), it is easy to see how failure to match ethnically alcoholic and control samples could produce an artifactual association. The need for ethnic matching is not specific to DRD$_2$. Ethnic variation in allele frequency is expected to characterize the vast majority of DNA polymorphisms, which have not been subjected to natural selection (Kidd 1993). Within-family controls are an effective way to control for ethnicity and other family environmental factors in an association study and had they been used in the DRD$_2$ studies, would likely have limited the number of reported positive associations (Hodge 1993).

Second, much of the controversy surrounding DRD$_2$ and alcoholism revolved around the clinical characteristics of the alcoholic and control samples. Alcoholism is a heterogenous disease. Variations in its expression are marked by differences in such features as drinking patterns, age of onset, and severity. Cloninger (1991) suggested that DRD$_2$ may be associated with severe alcoholism only and that failure to replicate the findings by Blum et al. (1990) may have resulted from the researchers' failure to accurately examine control samples of alcoholics. Given the marked heterogeneity that characterizes alcoholism, as well as the relatively high prevalence of the disorder, it is clear that future success with studies applying exacting molecular genetic techniques will depend on the availability of clinical samples that are carefully and comprehensively characterized.

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[a] Alleles are a series of two or more versions of the same gene that occupy the same position on a particular chromosome.

Finally, successful mapping of the genes contributing to alcoholism is likely to require a large family data base, access to a rich library of genetic markers, and the application of powerful methods of data analysis (Lander and Schork 1994). Although a systematic attempt to identify the genes contributing to alcoholism risk will require a substantial effort, such as the ongoing Collaborative Study on the Genetics of Alcoholism (COGA), the resources and conditions needed to ensure the success of such an enterprise are now technically attainable.

Influence of Alcohol Metabolizing Genes

Alcohol is metabolized principally in the liver by two enzymes that act sequentially. Alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde; aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate (figure 3). Genetic variations are associated with both enzymes.

Individuals within certain Asian populations experience a flushing reaction after consuming alcohol (Wolff 1972). The reaction is an unpleasant response to drinking that is characterized by facial flushing, headache, palpitations, dizziness, and nausea. This response to drinking is associated with an inactive variant of ALDH that allows acetaldehyde to accumulate in the blood and tissues after drinking (Thomasson et al. 1993). Compared with other ethnic groups, people of Asian descent experience lower rates of alcoholism and higher rates of abstinence (Helzer et al. 1990; Klatsky et al. 1983), and some scientists have suggested that the flushing reaction may serve to protect these individuals from heavy drinking and alcohol problems. Approximately 50 percent of Chinese and Japanese, but only 2 percent of Chinese and Japanese alcoholics, inherit the inactive form of aldehyde dehydrogenase (ALDH2) (Harada et al. 1982). The mutant (inactive) and wild-type forms of the *ALDH2* allele have been designated *ALDH2*^{2} and *ALDH2*^{1}, respectively. Although ALDH2 deficiency can help explain differences in alcoholism rates within East Asiatic populations and between East Asiatic and non-East Asiatic populations, the virtual absence of inherited ALDH2 deficiency among individuals of European and African ancestry indicates that it cannot help account for alcoholism rates within or between these populations (Agarwal and Goedde 1989).

> *Some scientists have suggested that the flushing reaction may serve to protect these individuals from heavy drinking and alcohol problems.*

Figure 3. The pathway of alcoholism metabolism.

Once in the liver, alcohol is converted into acetaldehyde and the acetaldehyde is converted into acetate. The enzyme alcohol dehydrogenase (ADH) catalyzes the first half of alcohol metabolism; the enzyme aldehyde dehydrogenase (ALDH) catalyzes the second half.

$$\text{Ethanol} \underset{\text{ADH}}{\rightleftharpoons} \text{Acetaldehyde} \xrightarrow[\text{ALDH}]{} \text{Acetate}$$

Genetic variation in ADH also may moderate the relationship between ALDH2 deficiency and alcohol consumption. High ADH activity, like low ALDH activity, could produce relatively high levels of acetaldehyde in the blood after drinking and perhaps could heighten the expression of the unpleasant symptoms of the flushing reaction. There are six genes for human ADH (*ADH1* to *ADH6*). Researchers have identified genetic variants for only *ADH2* and *ADH3*, with the *ADH2*^{2} and *ADH3*^{1} alleles encoding the high activity form of ADH. In a comparison of Chinese alcoholics and nonalcoholics, Thomasson et al. (1991, 1993) reported that the frequency of both the *ADH2*^{2} and the *ADH3*^{1} alleles was significantly higher among Chinese nonalcoholics than among Chinese alcoholics. Although the influence of polymorphisms at ADH appears to be weaker than those at ALDH, genetic variation in both of the major metabolic enzymes has been associated with alcoholism risk.

Despite a person's genetic constitution, it appears that culture may influence the relationship between ALDH2 deficiency and alcohol consumption. Korean, Japanese, and Chinese populations have similar rates of ALDH2 deficiency (Goedde et al. 1992). A recent cross-national study, however, reported that Korean men had higher rates of DSM-III-R alcohol abuse, alcohol dependence (42.8 percent), or both than any of the other four groups studied (the next highest rate being 31.0 percent among men from St. Louis, Missouri) (Helzer et al. 1990). Even though the relatively high rates of ALDH2 deficiency and alcoholism among Koreans was observed at the population level, rather than at the individual level, the study strongly suggests that the physiologically toxic effects of ALDH2 deficiency can be overcome by cultural factors that encourage heavy drinking (Reich and Li 1994).

Additional support for this proposition is found in a recent study exploring the relationship between fast flushing (similar to typical flushing) and drinking behavior among a general community and a college sample of Japanese-Americans living in southern California (Nakawatase et al. 1993). In both samples, self-reported fast flushing was associated with reduced rates of ever having drunk heavily (i.e., six or more drinks within a 24-hour period). However, a comparison of the protective effects of fast flushing across samples produced an interesting contrast. Only 14.5 percent of individuals in the general community sample who experienced a fast-flushing response reported ever having drunk heavily compared with 53.7 percent in the sample of college students. The researchers hypothesized that social pressures, alcohol availability, and freedom from parental monitoring in a college environment may all work to attenuate, but not fully ameliorate, the protective effects of fast flushing.

The genetically influenced traits thought to underlie responses to alcohol are called quantitative traits, and more than one gene influences the magnitude of a trait.

Of note, however, are findings reported by Tu and Israel (1995). These researchers noted that Asian males born in Canada or the United States with the inactive ALDH2 allele (and therefore would experience the flushing reaction after drinking) drank two-thirds less alcohol and were three times more likely to be abstainers than Asian males with the active ALDH2 allele. Acculturation of Asians in this study population accounted for only 7 to 11 percent of the variance in overall alcohol consumption.

Genetic Studies With Animal Models

Animal models of alcoholism are proving to be instrumental in identifying potential genetic factors that confer predisposition to alcoholism. Such models are enabling researchers to perform controlled analyses of genetically influenced biological traits or behaviors, such as alcohol consumption and preference, innate sensitivity or tolerance to alcohol, and metabolic rate of alcohol elimination, that are believed to resemble aspects of human alcoholism. Animal studies are an integral part of alcohol research because data from these studies potentially can inform alcoholism studies in humans. To date, this line of research has not yet revealed the genes responsible for alcohol-related behaviors. However, it has established that alcohol-related traits are determined by multiple genes and that the individual traits studied are, for the most part, determined independently of one another.

The role of genetics in alcohol-related behaviors is supported by selective breeding studies in animals, which have produced genetic lines differing in several alcohol-related traits. These lines include alcohol-preferring and alcohol-nonpreferring rats (selected for preference drinking) (Li et al. 1981); long-sleep and short-sleep mice (selected for differences in sensitivity to alcohol's anesthetic effect) (McClearn and Kahihana 1981); withdrawal-seizure-prone and withdrawal-seizure-resistant mice (selected for differences in severity of withdrawal after chronic alcohol administration) (Crabbe et al. 1985); HOT and COLD mice (selected for differences in sensitivity to alcohol-induced hypothermia) (Crabbe et al. 1989); and FAST and SLOW mice (selected for differences in sensitivity to alcohol-induced activity, a possible animal model of the euphoric effects of alcohol in humans) (Crabbe et al. 1987). The ability to breed lines of animals with high or low measures of these traits indicates that they are influenced by genetic factors.

Quantitative Trait Loci Analysis

As noted earlier, alcoholism is a polygenic disorder, influenced by many genes located in different areas of a person's or an animal's DNA (Goldman 1993; McClearn et al. 1991). The genetically influenced traits thought to underlie responses to alcohol are called quantitative traits, and more than one gene influences the magnitude of a trait. Within a population, a quantitative trait varies continuously in its degree of expression. A section of DNA on a chromosome thought to influence a quantitative trait is known as a quantitative trait locus (QTL).

With the recent increase in the density of markers identified on the mouse genetic map (Dietrich et al. 1995) and the development of new and more powerful methods of data analysis (Jansen and Stam 1994; Zeng 1994), researchers now have the tools to map individual QTL. QTL mapping is challenging because each QTL may have only a small effect on the quantitative trait under examination. Once a QTL has been identified, however, the gene can be isolated and its functions can be studied in detail. Thus, QTL mapping and analysis enables researchers to locate and measure the effects of a single QTL on a trait (phenotype) (Grisel and Crabbe 1995) and, ultimately, to gain knowledge of the complex physiologic underpinnings of alcohol-related behavior.

An important tool in QTL analyses is the recombinant inbred (RI) mouse strain. RI mouse strains enable researchers to compare different strains of mice in which all animals of a strain were produced from a population of second-generation, or F2, offspring of two genetically distinct parental, or progenitor, inbred strains. In the RI method, the members of a single strain are inbred to be genetically identical; that is, every individual within a strain has the same alleles at all loci. The process of generating RI strains begins with the mating of two inbred mouse strains to produce first generation (F_1) animals (figure 4). F_1 animals are mated, and through recombination of genetic material, each F_2 mouse inherits a distinctive combination of genes from the two progenitor strains. Sister-brother pairs of F_2 are then mated to "fix" the unique pattern of recombinations. Their offspring are inbred for many generations, thus producing an RI strain of mice that are identical at each locus. Alcohol experiments commonly have used the BXD Recombinant Inbred mouse strains.

Such findings suggest that preference for alcohol may be controlled by different genetic mechanisms in males and females.

A QTL analysis is generally performed by correlating statistically the differences in alleles of particular genetic markers with differences in phenotypes in a population. More than 1,500 markers have been identified for the BDX RI strains, a feature that makes these mouse strains particularly useful to QTL studies. Alcohol-related phenotypes also have been identified and recorded for the progenitor and the BDX RI strains. By comparing the phenotypes for each strain with the pattern of genetic markers for that strain, researchers can determine if relationships exist between particular phenotypes and markers.

Only recently have alcohol researchers begun to use and gather results from QTL analysis. Crabbe et al. (1994) found that sensitivity to alcohol-induced hypothermia (a drop in body temperature after alcohol administration) was associated with the marker *D1Byu7* on chromosome 1, which is proximal to the *Ltw-4* gene on the mouse chromosome. The *Ltw4* gene codes for a protein that is abundant in the brain, liver, and kidney and is associated with alcohol consumption, amphetamine-induced hyperthermia, and withdrawal from some central nervous system depressants. Although researchers have yet to determine how the Ltw protein may influence these traits, the *Ltw-4* gene is now considered a candidate gene and can be studied in more detailed analyses.

In their QTL analysis of alcohol-induced hypothermia, Crabbe et al. (1994) also found that animals' hypothermic sensitivity correlated with two closely associated markers on chromosome 9. These markers are located in the same region as the gene for the serotonin $5HT_{1B}$ receptor. To test whether serotonin activity at this receptor plays a role in the hypothermic response, the investigators studied "knockout"[5] mice in which the gene for the $5HT_{1B}$ receptor was mutated, thus preventing the encoding of a functional receptor. The mice lacking the $5HT_{1B}$ receptor were less sensitive to alcohol-induced hypothermia than normal mice, providing further evidence that activity at this receptor may contribute to the hypothermic response to alcohol. In a more recent study of these knockout mice, Crabbe et al. (1996) observed that the mutant mice drank twice as much alcohol as the normal mice. This finding suggests that the $5HT_{1B}$ receptor also participates in the regulation of alcohol intake and that mice lacking the receptor are less sensitive to alcohol's effects, leading to a loss of regulation of drinking.

Melo et al. (1995) recently identified two loci, namely *Alcp1* and *Alcp2*, with significant effects on the consumption of alcohol by mice. The *Alcp1* locus, which maps to chromosome 2, acts only in males; the *Alcp2* locus, which maps to chromosome 11, acts only in females. Such findings suggest that preference for alcohol may be controlled by different genetic mechanisms in males and females. Although these results are interesting, additional research is needed to

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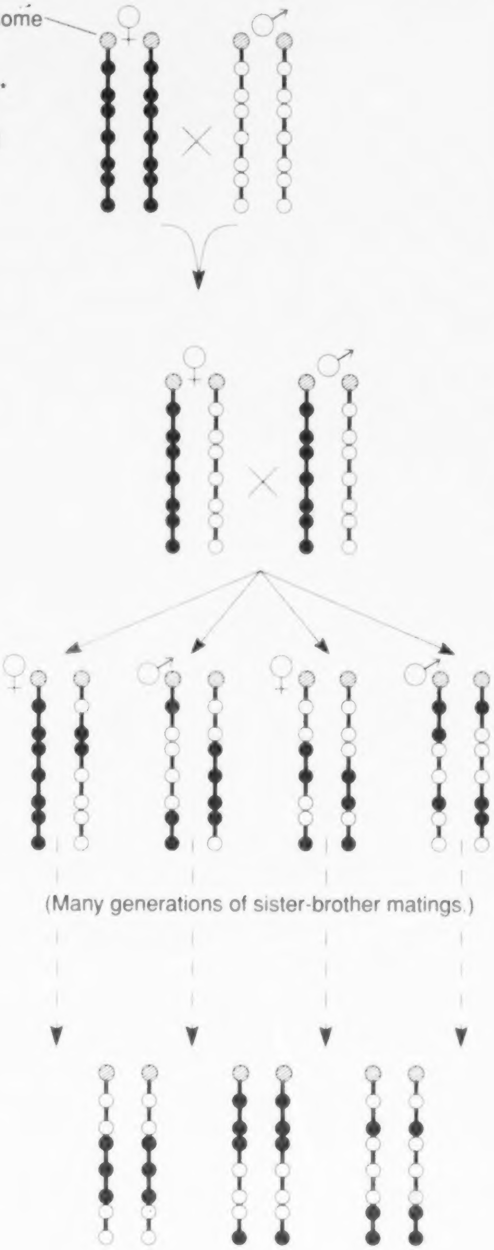
[5] The technology used to prepare knockout mice enables researchers to change, or mutate, a targeted gene to prevent it from encoding a functional product. The mutated gene is then transferred into embryonic stem cells, which, in turn, are injected into a mouse embryo at an early stage of development.

Figure 4. The process of deriving recombinant inbred (RI) strains.

An example for one chromosome pair is shown. Two parent inbred strains are depicted. Although DNA with multiple forms is distributed throughout the entire set of an animal's genetic material, for the purposes of illustration, DNA specific to one is shown in black, and DNA specific to the other is depicted in white (shared regions are patterned).

Fixed location on a chromosome (i.e., the centromere).

Single chromosome pair* (e.g., chromosome 1) from each of two parent (i.e., progenitor) inbred strains.



Two inbred strains are mated to produce a first-generation (F_1) cross. Within an inbred strain, each individual has two copies of the same form (i.e., allele) of each gene. Alleles that differ between strains are shown as black and white regions. In reality, any two inbred strains differ at some percentage of the chromosome, randomly distributed across the complete set of chromosomes.

F_1 offspring are identical; at all areas of the chromosome where the progenitors differed, offspring receive one allele from each parent.

F_1 animals are mated to produce the second (F_2) generation.

Meiosis and crossing over produce chromosomes with different patterns in the F_2 mice. Therefore, the chromosomes in F_2 offspring show unique recombinations of genes.

Several sister-brother F_2 pairs are then mated. This inbreeding is repeated for many generations, eventually resulting in animals that are genetically identical for one or the other progenitor's alleles at all locations on the chromosomes (i.e., resulting in many unique RI strains).

*Chromosomes are lengths of DNA that contain genes and compose most organisms' genetic material. Chromosomes in cells are paired. One chromosome of the pair is inherited from the organism's father, and the other is inherited from the mother.
Source: Grisel and Crabbe 1995.

replicate whether the genetic influence for alcohol preference is affected by gender.

An important advantage of QTL and phenotypic data from RI strains is that they can be accumulated and reanalyzed as the marker map increases in density. Furthermore, in addition to identifying chromosomal regions containing important genes for single phenotypes, comparisons of QTL results across phenotypes can provide clues about the commonality of genetic systems determining two or more responses. Plomin et al. (1991) have created an RI QTL cooperative data bank, which could greatly enhance the comparisons that could be made among alcohol as well as nonalcohol phenotypes.

Individuals with a lower intensity reaction to alcohol's effects may be at relatively high risk for alcoholism because they lack effective feedback mechanisms that signal overconsumption.

Individual-Level Factors That Affect Drinking Behavior

Identifying the specific genes that are involved in the etiology of alcoholism will represent a major scientific breakthrough for the field, yet it is important to recognize that no gene exists with the primary function to make its possessor drink chronically and abusively. Genetic factors exert their influence on human drinking behavior indirectly, through multiple biochemical, physiologic, and psychological steps in a pathway that links primary gene products (protein synthesis) with overt behavior (drinking). Every step in this complex pathway is subject to external, environmental modulation. Understanding how genes influence risk of alcoholism ultimately will require integrating knowledge of specific genetic effects into a broader framework that considers the multiple factors that influence drinking behavior.

In considering the forces that affect drinking behavior, it is useful to distinguish between individual-level factors and contextual factors. Individual-level factors are the characteristics of an individual that either increase or decrease the likelihood that he or she will use or abuse alcohol. Alcohol researchers currently are investigating various classes of individual-level factors, including alcohol sensitivity, neurophysiologic processes, biochemical markers, personality characteristics, and cognitive processes. Contextual factors are social and cultural characteristics that either increase or decrease the likelihood an individual experiencing them will use or abuse alcohol. Although it is useful initially to distinguish these two types of influence, knowledge of the two must eventually be integrated into a general framework that reflects the factors' mutual dependence and potentially interactive effects.

Alcohol researchers use high-risk studies, which compare offspring of alcoholics with offspring of nonalcoholics, to identify and characterize individual-level factors that increase the risk for developing alcoholism. The well-established familial association with alcoholism indicates that, as a group, offspring of alcoholics are at relatively high risk for developing the disease. Accordingly, a factor that contributes to risk of alcoholism and, like alcoholism, is transmitted from one generation to the next, should differentiate between the offspring of alcoholics and nonalcoholics. In addition, studying offspring at an age before the onset of drinking factors enables researchers to identify the factors that are predictors, rather than consequences, of problem drinking.

Alcohol Sensitivity

People vary widely in their reactions to alcohol. For some, alcohol is activating and pleasurable; for others, it produces nausea and dysphoria. Given the wide range of individual reactions to alcohol, it seems probable that individual differences in alcohol sensitivity could influence differences in drinking behavior and alcoholism risk. Numerous investigators have compared the reactions to alcohol in offspring of alcoholics and offspring of nonalcoholics to determine whether altered alcohol sensitivity is an inherited risk factor for alcoholism (see Newlin and Thomson 1990 and Pollock 1992 for reviews). Unfortunately, most of the research in this area has been conducted in men. Thus, the relevance of altered alcohol sensitivity to the inheritance of alcoholism in women cannot be evaluated at this time.

Schuckit (1994*a*) proposed a prominent model relating alcohol sensitivity to alcoholism risk based on findings from previous studies. For example, Schuckit and Gold (1988) noted that 40 percent of the sons of alcoholics compared with fewer than 10 percent of the sons of nonalcoholics studied demonstrated low levels of reaction to alcohol after receiving moderately intoxicating amounts of the beverage. Individuals with a lower intensity reaction to alcohol's effects may be at relatively high risk for alcoholism because they lack effective feedback mechanisms that signal overconsumption. They also may be at risk because they drink more than those who are highly sensitive to alcohol to achieve the same effects. The Schuckit model has been widely investigated, and the finding of reduced alcohol sensitivity among sons of alcoholics has been generally, although not universally, replicated by other investigators (Pollock 1992). Several questions about this model, however, have yet to be answered. For example, whether the observations reflect differences in sensitivity to alcohol or differences in acquired tolerance in the two populations studied is uncertain. In addition, the Schuckit model assumes that two measures of alcohol sensitivity, namely body sway and subjective intoxication, are heritable. Scientists have yet to determine whether this assumption is accurate.

> *Using an alternative experimental paradigm, Finn has proposed a model suggesting that sons of alcoholics demonstrate heightened sensitivity to alcohol's effects.*

Using an alternative experimental paradigm, Finn (Finn and Pihl 1987; Finn et al. 1990) has proposed a model suggesting that sons of alcoholics demonstrate heightened sensitivity to alcohol's effects. Stress-response dampening refers to the ability of alcohol to attenuate the body's natural response to an acute stressor. The alcohol-induced effect is thought to be a physiologic basis for what is widely believed: Alcohol can be used to relieve tension (Sher 1987). Several investigators have observed that after an intoxicating dose of alcohol and then exposure to a stressor, cardiovascular response to the stressor is significantly reduced among young nonalcoholic men with a multigenerational history of alcoholism (i.e., those having alcoholic biological relatives in at least two generations) compared with those with no family history of alcoholism (Finn and Pihl 1987; Finn et al. 1990; Stewart et al. 1992). Not all studies of sons of alcoholics, however, have reported a heightened stress-response dampening with alcohol exposure (Sayette 1993; Sayette et al. 1994); this inconsistency may stem from the studies' use of relatively low doses of alcohol or of subjects with a unigenerational, rather than multigenerational, family history of alcoholism (Stewart et al. 1992). Yet the implications of enhanced stress-response dampening among those with a family history of alcoholism are quite clear: Individuals at high risk for developing alcoholism may be more likely to abuse alcohol than those at low risk because their drinking is more likely to be reinforcing a reduction in stress. Among those with a family history of alcoholism, the effect of increased stress-response dampening may be further compounded by a heightened sensitivity to stress (Finn et al. 1992; Hill et al. 1992; Sayette 1993). Thus, those with a family history of alcoholism may be more likely to abuse alcohol because they are more likely to be hyperresponsive to stress and because the consumption of alcohol is more likely to dampen that response.

Newlin and Thompson (1990) have proposed a differentiator model that may account for the apparent incompatibility between the Schuckit and Finn models. The investigators reviewed studies comparing alcohol sensitivity among the sons of alcoholics and sons of nonalcoholics and plotted risk group differences as a function of time since alcohol ingestion. From this analysis, they noted that the sons of alcoholics tended to be more sensitive to the effects of alcohol as blood alcohol levels were rising and less sensitive as blood alcohol levels were falling. The differentiator model posits that the sons of alcoholics are at increased risk for developing alcoholism because they are hypersensitive to the pleasurable and activating effects of alcohol associated with rising blood alcohol levels and hyposensitive to the dysphoric and sedating effects of alcohol associated with falling blood alcohol levels. The differentiator model has received support in several recent investigations (Bauer and Hesselbrock 1993; Cohen et al. 1993), the specifics of which are discussed below.

When using a high-risk study design, researchers assume that the factors that differentiate the offspring of alcoholics from the offspring of nonalcoholics at the group level also predict the subsequent development of alcoholism at the individual level. In a recent publication, Schuckit (1994*b*) tested the validity of this assumption as it applies to his studies and model of alcohol sensitivity. Initial studies, conducted between 1978 and 1988, evaluated the reactions to alcohol in young sons of alcoholics (average age of 20 years) (Schuckit 1994*a*; Schuckit and Gold 1988). More recent investigations have used the same study population, now aged 30, to determine the relationship between reaction to alcohol and future risk for alcohol-related problems. In an analysis of data from the first 223 of 454 men to complete the nearly 10-year followup clinical assessment, Schuckit (1994*b*) reported that a higher percentage of the sons of alcoholics (34 percent) than the sons of nonalcoholics (13 percent) had developed alcoholism during the followup period. More significantly, compared with the nonalcoholic men, the men who developed alcoholism demonstrated lower sensitivity to alcohol 10 years earlier, prior to their onset of alcoholism. The reduced sensitivity was evident when assessed subjectively (e.g., by intoxication rating) and objectively (e.g., by body sway). The rate of alcoholism among the 20 percent of men who showed the weakest reaction to alcohol 10 years earlier was nearly 4 times greater than the rate of alcoholism observed among the 20 percent of men with the strongest reaction. In a recent followup of this study population, Schuckit and Smith (1996) concluded that alcohol sensitivity at age 20 was associated with future alcoholism, regardless of drinking practices at the time of the original study, and that alcohol sensitivity among men with the highest and lowest scores for this measure may, in general, be a mediator of alcoholism risk.

Individuals at high risk for developing alcoholism may be more likely to abuse alcohol than those at low risk because their drinking is more likely to be reinforcing a reduction in stress.

Neurophysiology

Event Related Potentials

Evidence that alcohol produces marked effects on the central nervous system has prompted researchers to explore whether changes in various neurobehavioral functions may reflect vulnerability for alcoholism. Toward this goal, researchers have examined measurements of the event related potential (ERP) of the brain, and specifically the amplitude of the P300 (or P3) component of the (ERP), as potential neurophysiologic markers of alcoholism liability. The P300 is a positive peak of the ERP wave-form that occurs approximately 300 milliseconds after an informative event and is thought to be associated with various cognitive activities, such as information processing, decisionmaking, and memory (Donchin and Coles 1988). In a landmark study, Begleiter et al. (1984) reported that the amplitude of visually elicited P300 was reduced in a sample of 7- to 13-year-old sons of alcoholics compared with an age-matched sample of sons of nonalcoholics.

The possibility that P300 amplitude might provide a biological measure that prospectively marked an individual's risk for alcoholism drew much interest from alcohol researchers. Several laboratories were able to replicate the findings of Begleiter and his colleagues. Other investigators, however, failed to observe the expected differences in P300 amplitude between high-risk and low-risk study participants (Hill et al. 1988; Lille et al. 1987; Polich and Bloom 1988).

This apparent inconsistency in findings was recently addressed in a meta-analysis[6] of the literature by Polich et al. (1994). The researchers examined 22 investigations focused on the relationship between P300 amplitude and risk for alcoholism. Unfortunately, at the time of the review, published research on P300 amplitude in daughters of alcoholics was scarce, and thus the investigators were able to only review studies based on samples of males. They found that, overall, males with a positive family history of alcoholism had moderately smaller P300 amplitudes than males with a negative family history of alcoholism (average effect size of 0.33). Differences in stimulus presentation in the various studies may have contributed to the failure by some groups to replicate the basic finding. Significant differences in P300 amplitude in high-risk and low-risk groups were found only when a visual stimulus, rather than an auditory stimulus, was used and only when the stimulus discrimination task was difficult, rather than easy. The average effect size was 0.65 for the nine investigations which, like the original study by Begleiter et al. (1984), used a visual stimulus and a difficult discrimination task.

Given that P300 is thought to measure attentional and memory processes, the relationship of P300 amplitude to alcoholism risk may reflect differences in cognitive ability between high-risk and low-risk groups.

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[6] The method of meta-analysis was developed to provide a quantitative alternative to the traditional approach for a literature review (Hedges and Olkin 1985). In a meta-analysis, research findings are summarized in terms of an average effect size (in the present context, the average mean difference between alcoholism risk groups in standard deviation units), and design factors that moderate the magnitude of this statistical effect are identified.

This possibility is supported by research documenting neuropsychological differences between the offspring of alcoholics and the offspring of nonalcoholics (Parsons et al. 1990). An alternative explanation for the association between P300 amplitude and alcoholism risk is suggested by the meta-analysis of the P300 literature (Polich et al. 1994). During adolescence, the average amplitude of P300 increases with age of the study participants, and thus P300 may be considered a marker for neurological development. In the meta-analysis, age significantly influenced the association between P300 amplitude and risk status. The average effect size was 0.62 for participants aged 17 years or younger compared with 0.16 for participants aged 18 years or older. These findings raise the possibility that the association of P300 amplitude with alcoholism risk reflects a delay in neurological development and cognitive functioning among young sons of alcoholics compared with sons of nonalcoholics (Hill 1995).

The heritability of P300 is one of the main assumptions underlying use of this measure as a biological marker for alcoholism risk. To test this assumption, O'Connor et al. (1994) studied a sample of 59 identical and 39 fraternal twin pairs and reported that the P300 amplitude elicited in response to an unusual auditory stimulus was significantly and substantially heritable. These findings were extended to include visually evoked P300 in a study of 30 identical and 29 fraternal twin pairs (Katsanis et al. in press). In the latter study, P300 amplitude was consistently found to be heritable. Moreover, the heritability of P300 amplitude was greater when the stimulus condition task was difficult (average heritability of 0.64) than when it was easy (average of 0.52). The study by Katsanis et al. (in press) suggests that the heritability of P300 amplitude appears to be maximized under the experimental conditions (e.g., a visual stimulus and relatively difficult discrimination task) that also maximize the difference in P300 amplitude between the sons of alcoholics and the sons of nonalcoholics.

Although most of the research on P300 amplitude and alcoholism risk has been conducted in men, several recent studies have addressed the relevance of P300 for women. Hill and Steinhauer (1993) reported that female alcoholics, like male alcoholics, show significant deficits in P300 amplitude compared with nonalcoholic controls. In addition, daughters of alcoholic mothers display reduced P300 amplitude, suggesting that the neurobiological indicators of risk are the same in sons of alcoholic fathers and daughters of alcoholic mothers (Hill et al. 1995*a*). Whether the diminished P300 amplitude observed in female children of alcoholic mothers is associated specifically with alcoholism or is a general marker of adult psychopathology still remains to be determined. In male children, however, evidence suggests that reduced P300 amplitude is a neurobiological marker for alcoholism risk: An 8-year followup study of children from male alcoholic families found a relationship between P300 amplitude at age 10 and alcohol dependence at followup (Hill et al. 1995*b*).

Electroencephalogram

Studies of baseline (prealcohol) electrical brain activity, as measured by an electroencephalogram (EEG), indicate that alcoholics show reduced activity in the alpha range of frequency bands of brain waves and increased activity in the theta, delta, and beta ranges (Begleiter and Platz 1972; Volavka et al. 1985). Studies of the male sons of alcoholics and nonalcoholics, however, have not consistently found risk group differences in baseline EEG frequency bands (Cohen et al. 1991). Bauer and Hesselbrock (1993) have argued that the inconsistency of findings with EEG may be due to failure to consider the possible moderating effects of comorbid psychopathology, specifically antisocial personality disorder (ASPD). From their own research on baseline EEG, Bauer and Hesselbrock (1993) did find an association between a positive family history of alcoholism and increased beta activity, but this association held only when the males with a positive family history also met diagnostic criteria for ASPD.

Although the existing literature does not allow unequivocal conclusions about the relationship between vulnerability to alcoholism and baseline EEG, studies have provided more consistent evidence for a correlation between alcoholism risk and changes in EEG after alcohol ingestion. Cohen et al. (1993) reported that after alcohol ingestion, sons of alcoholic fathers demonstrated significantly greater increases in slow alpha activity with rising blood alcohol levels and faster recovery of baseline slow alpha activity with falling blood alcohol levels than did sons of nonalcoholic fathers. Bauer and Hesselbrock (1993) reported very similar findings with fast alpha activity; that is, greater sensitivity among sons of alcoholics during rising blood alcohol levels and greater recovery during falling levels. This finding corresponds with changes in sensitivity to alcohol that are proposed by Newlin and Thomson's differentiator model.

A study of 19-year-old sons of alcoholics and sons of nonalcoholics explored whether familial risk and greater EEG sensitivity to alcohol can predict future development of alcoholism (Volavka et al. 1996). Findings suggested that although greater EEG response at age 19 was not related to risk for developing alcoholism, a smaller EEG alpha frequency response to alcohol at 19 years was associated with the development of alchohol dependence and heavy drinking 10 years later. The findings were based on a small group of subjects and thus are somewhat preliminary, but they suggest that lower EEG response to small doses of alcohol may be associated with later development of alcoholism.

Biochemical Factors

An important direction of alcohol research is the search for biochemical factors, or markers, that can identify individuals who are at high and low risk for developing alcoholism. In searching for biochemical predictors of alcoholism, researchers have focused first on neurotransmitter systems that either interact with alcohol or have been implicated through animal studies in alcohol self-administration. For example, recent work has explored the role of the serotonin neurotransmitter system and the enzyme monoamine oxidase (MAO).

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Serotonin Neurotransmitter System

Research evidence suggests that alcoholism may be related to serotonin levels in the brain (Litten and Allen 1991). Serotonin, a neurotransmitter that regulates such functions as bodily rhythms, food and water intake, sexual response, and response to pain, has been linked to impulsive aggression and disruptive behavioral disorders (Zubieta and Alessi 1993). On average, alcoholics compared with nonalcoholics have lower levels of platelet serotonin and of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid. The observed deficiency in serotonin function persists even after 2 weeks of abstinence from alcohol (Bailly et al. 1993). Serotonin deficiency also characterizes young adult nonalcoholics who have a positive family history of alcoholism (Rausch et al. 1991), suggesting that serotonin dysfunction is a predictor rather than a consequence of alcohol abuse.

Serotonin dysfunction could contribute to alcohol overconsumption in several ways. For example, low levels of serotonin are associated with increased appetitive motivation and impulsive behavior, and individuals who are deficient in serotonin may find drinking more inviting and more difficult to stop once started than individuals with normal levels of serotonin (Spoont 1992). Alternatively, alcohol consumption produces a temporary increase in serotonin levels, but chronic depletion and this effect of alcohol could reinforce chronic alcohol overconsumption in individuals with low levels of serotonin (Bailly et al. 1993).

Serotonin dysfunction may be specifically implicated in type II alcoholism, a subtype of alcoholism that, when compared with other forms, is characterized by an earlier age of onset of alcohol problems, more social and legal consequences, and a greater genetic predisposition for its development (Cloninger 1987). (See the *Eighth Special Report to the U.S. Congress on Alcohol and Health* for a full discussion of research on subtypes of alcoholism.) Virkkunen and Linnoila (1993) found significantly lower levels of 5-HIAA in the cerebrospinal fluid of alcoholics who had committed impulsive violent crimes than in healthy controls and alcoholics who had committed crimes that were violent but not impulsive. Cerebrospinal fluid levels of 5-HIAA were also correlated with a personality measure of aggressive inhibition. Thus, for early onset alcoholics with impulsive tendencies, alcohol may interact with depleted levels of serotonin to increase the likelihood of aggression (Pihl and Peterson 1993).

Monoamine Oxidase Activity

Enzymes have received much attention in the search for genetic markers for alcoholism. Because enzymes are direct products of genes, variations in their properties can be traced easily to corresponding genes. Moreover, selected enzymes are associated with mechanisms and sites in the body that are affected by alcohol. Thus, enzymes are an important focus of studies exploring biological markers for alcoholism.

Many studies have investigated whether MAO is a possible marker for susceptibility to alcoholism. MAO is involved in the breakdown of monoamine neurotransmitters (i.e., dopamine, serotonin, and norepinephrine), which have been implicated in phenomena related to risk for alcoholism. Two forms of the enzyme, namely MAO-A and MAO-B, have been identified in human brain. The MAO-B form also is found in platelets; because platelets are more accessible than the brain for experimental testing, platelets are typically studied as a surrogate for brain MAO-B in human behavioral studies.

Some studies have shown that alcoholics and the first-degree relatives of alcoholics have relatively low levels of platelet MAO activity, suggesting that MAO activity is an inherited biochemical risk factor for alcoholism; other studies, however, have shown no such association (Eskay and Linnoila 1991; Sher et al. 1994). Low platelet MAO activity appears to correspond to high impulsivity and sensation seeking (Sher et al. 1994), suggesting that it may be a marker for type II alcoholism. Indeed, some studies have shown that male type II alcoholics exhibit lower platelet MAO activity levels than male type I alcoholics and nonalcoholic controls (von Knorring et al. 1991). A recent finding from the ongoing COGA project showed that, regardless of the alcoholism subtyping used to analyze study participants (i.e., type I versus type II, type A versus type B), men with an earlier onset and a more severe course of alcohol problems had significantly lower platelet MAO activity than nonalcoholic men (Anthenelli et al. in press).

No evidence suggests that there is a personality profile that uniquely characterizes alcoholics; however, alcoholics and nonalcoholics differ on certain personality scores.

Researchers have begun to question whether reduced MAO activity also is associated with alcoholism in females. Hallman et al. (1990) reported that reduced MAO activity did differentiate female alcoholics from female nonalcoholics. Nonetheless, the magnitude of the difference between female alcoholics and nonalcoholics may be smaller than the difference observed with males (see Hallman et al. 1991 for a review). Moreover, the expected personality and clinical correlates of low MAO were not observed among the female alcoholics, suggesting that the effects of low MAO may be different for men and women.

Reduced MAO activity level and its influence on vulnerability to alcoholism may be associated with the role of serotonin in the development of disease. Because individuals with low platelet MAO activity levels have low levels of degradation products from serotonin in their cerebrospinal fluid, Oreland and Shaskan (1983) suggested that low MAO activity actually may reflect low serotonin turnover in cerebrospinal fluid. As noted earlier, serotonin levels frequently are reduced in people with early onset alcoholism and related personality traits (Virkkunen and Linnoila 1993). These observations suggest that low platelet activity is a peripheral marker for altered serotonin function, which in turn could contribute to vulnerability to alcoholism (Anthenelli and Tabakoff 1995).

Although the possible influence of MAO activity on alcoholism risk continues to be actively investigated (e.g., Devor et al. 1993), some evidence suggests that this biochemical factor may not be a specific marker for alcoholism. For example, Anthenelli et al. (in press) noted that various factors, including psychiatric and medical illness, metabolic factors, personality traits, cigarette smoking, and other drug use, can influence platelet MAO activity. Thus, whether the relatively low levels of MAO activity observed among alcoholics may be a secondary consequence of recent alcohol consumption (Giller and Hall 1983; Goldman 1993) or cigarette smoking (Anthenelli et al. in press) or a general indicator of a spectrum of disorders marked by disinhibition, impulsive aggression, and a predisposition for alcohol and other drug use (Anthenelli et al. 1995; Sher et al. 1994) awaits further investigation.

Personality

No evidence suggests that there is a personality profile that uniquely characterizes alcoholics (i.e., the "alcoholic personality"; Nathan 1988); however, alcoholics and nonalcoholics differ on certain personality scores (Graham and Strenger 1988). In some cases, these personality differences predate the onset of alcoholism (e.g., Zucker and Gomberg 1986) and also serve to differentiate adolescent children of alcoholics from adolescent children of nonalcoholics (Sher 1991). Although alcoholics and nonalcoholics and adolescents at high and low risk for developing alcoholism differ only modestly in measures of personality differences, these findings suggest that selected personality factors may contribute to risk for the development of alcoholism.

Alcoholism and alcoholism risk most consistently have been associated with two broad dimensions of personality. The first personality dimension, which has been variously termed behavioral disinhibition, behavioral undercontrol, or deviance proneness (Sher 1991), reflects an individual's inability or unwillingness to inhibit behavioral responses to cues of impending punishment (Gorenstein and Newman 1980). Specific indicators of this dimension include impulsivity, unconventionality, overactivity, and aggression. The second personality dimension, which has been termed negative emotionality or neuroticism, refers to an individual's propensity to experience negative mood states or psychological distress. Specific indicators of this second dimension include emotionality, neuroticism, depression, and anxiety. Recent research on the relationship between personality and alcohol use has focused on characterizing the processes by which these personality factors influence drinking behavior and determining how the effect of these personality factors interact with other known risk factors for alcoholism.

A childhood history of hyperactivity is predictive of alcohol abuse in adolescence only when accompanied by a history of conduct disorder.

Although alcoholics and individuals at risk for developing alcoholism consistently score higher than nonalcoholics on indicators of behavioral undercontrol (Sher and Trull 1994), some researchers have suggested that these relationships may reflect the well-established association between antisocial behavior and abusive drinking rather than a specific influence of personality on drinking behavior. For example, in a sample of nonalcoholic men aged 21 to 25 years, Hesselbrock and Hesselbrock (1992) reported that the personality traits of impulsivity, novelty seeking, and sensation seeking were associated with ASPD but not otherwise associated with a family history of alcoholism. Similarly, a childhood history of hyperactivity (a clear indicator of behavioral undercontrol) is predictive of alcohol abuse in adolescence only when accompanied by a history of conduct disorder (i.e., antisocial behavior) (Mannuzza et al. 1993; Pihl and Peterson 1991).

Even if antisocial behavior influences entirely the relationship between behavioral undercontrol and alcohol abuse, the introduction in research of the personality concept of behavioral control has been useful in conceptualizing the process by which antisocial behavior and alcohol abuse become linked. Because they are less likely to be affected by cues of punishment, children who are highly impulsive, aggressive, and overactive can be more difficult for their parents and teachers to socialize than children who are controlled and compliant (Finn et al. 1994). The possession of a "difficult temperament" (Windle 1991) in combination with ineffective parenting is likely to produce an orientation toward deviant peers and away from parents, school achievement, and acceptance of societal norms (Sher 1994), factors that will all increase the likelihood of alcohol abuse.

With respect to negative emotionality (the second broad dimension of personality), individuals who score high on measures of this personality dimension are more likely than those who score low to experience psychological distress (often referred to as "anxiety" in the literature). Some evidence indicates a modest association between such anxiety and drinking behavior (e.g., Swaim et al. 1989). The modest relationship between anxiety and alcohol consumption may reflect the general unimportance of negative mood state in determining drinking behavior. Or, the modest association may arise because anxiety is an important influence on drinking behavior for a subset of drinkers. Recent research has provided support for this second alternative.

In a survey of college students, Kushner et al. (1994) found that expectations about the use of alcohol to relieve tension influenced the relationship between self-reported anxiety and drinking behavior in men only. Anxiety and drinking behavior were positively associated in men who believed strongly that alcohol could reduce tension, but were negatively associated in men who had relatively weak beliefs about the tension-reduction properties of alcohol. This gender difference replicates an earlier study by Cooper et al. (1992), who reported that alcohol expectancies affected the relationship between negative life events and alcohol use in men but not women. It may be that a strong belief in alcohol's anxiolytic properties can reinforce alcohol use in men, whereas women who are experiencing psychological distress may associate alcohol use with loss of control and increased vulnerability (Kushner et al. 1994).

The relationship between psychological distress and drinking also may be influenced by other personality factors. Hussong and Chassin (1994) investigated whether impulsivity, an indicator of behavioral undercontrol, potentiated the relationship between negative emotionality and alcohol use in a sample of adolescents. They observed that self-reported depression was more strongly related to heavy alcohol use among adolescents who were highly impulsive than among adolescents who were not impulsive.

Cognitive Factors

Alcohol researchers studying cognitive factors have emphasized the importance of learning in the development and maintenance of drinking styles (Wilson 1987). Alcohol expectancies, the beliefs that individuals hold about the anticipated consequences of drinking, figure prominently in current cognitive models of alcohol use and abuse. Previous research has demonstrated that alcohol expectancies differentiate alcoholics from nonalcoholics, are strongly correlated with current and future alcohol consumption in all age groups (Reese et al. 1994; Stacy et al. 1991), appear to develop before initial exposure to alcohol and are thus not simply a consequence of direct experience with alcohol (Noll et al. 1990), are associated with personality indicators of behavioral undercontrol (Henderson et al. 1994; Mann et al. 1987; Sher et al. 1991), and may influence in part the relationship between family history of alcoholism and alcohol use (Sher et al. 1991). Moreover, particular alcohol expectancies (e.g., enhancement of sexual experience) are associated specifically with alcohol use in particular contexts (e.g., before sexual intercourse; Dermen and Cooper 1994), suggesting that alcohol expectancies provide a critical motivational basis for drinking. In short, alcohol expectancies are thought to represent a final common pathway mediating the influences of various biological, psychological, and social factors on drinking behavior (Goldman and Rather 1993).

In short, alcohol expectancies are thought to represent a final common pathway mediating the influences of various biological, psychological, and social factors on drinking behavior.

The research literature linking alcohol expectancies with drinking behavior is substantial and consistent, yet the relevant evidence has been overwhelmingly correlational in nature. In an attempt to confirm that alcohol expectancies can directly influence drinking behavior, Darkes and Goldman (1993) found that male college students significantly reduced their drinking after exposure to an intervention aimed at changing their alcohol expectancies. The investigators observed the greatest reductions in drinking among the heaviest drinkers. In contrast, they noted no significant changes in drinking practices for the male college students randomly assigned either to the no-treatment control group or to a group that received a traditional information-based intervention aimed at reducing drinking behavior. The study confirms that experimental manipulation of expectancies can affect subsequent drinking behavior and suggests that cognitively based interventions might prove more effective in reducing drinking than traditional interventions.

Recent research indicates not only that heavy drinkers anticipate greater benefit from drinking than light drinkers but also that the accessibility and organization of alcohol expectancies in memory differ for heavy and light drinkers. Rather and Goldman (1992, 1994) explored the memory representations of alcohol expectancies by having drinkers judge the likely co-occurrence of drinking with various effects of alcohol. They reported that although the alcohol expectancies of heavy drinkers were tightly associated in memory and focused on the arousing and positive effects of drinking, the alcohol expectancies of light drinkers were loosely associated and focused on the sedating and positive outcomes of drinking. Similarly, Stacy et al. (1994) found that heavy drinkers were more likely than light drinkers to spontaneously associate drinking with positive outcomes that are potentially, but not necessarily, linked to drinking (e.g., feeling relaxed or having fun with friends). These findings from nonexperimental studies are consistent with results from experimental research that demonstrate that an alcohol cue elicits a more rapid, salient, and longer lasting desire to drink in heavy as compared with light drinkers (Greeley et al. 1993). In short, there is a convergence of evidence suggesting that an alcohol stimulus increases the likelihood of consumption among heavy drinkers because it is rapidly associated with multiple positive and arousing outcomes, but it inhibits consumption among light drinkers because it activates only a few associations and these associations encompass the sedative as well as positive effects of drinking (Goldman and Rather 1993).

Sociocultural and Contextual Influences on Drinking Behavior

The evidence implicating genetic and individual-level factors as influences on alcoholism and drinking behavior is consistent and compelling. Equally compelling is the evidence that the cultural, social, and historical context of individuals' lives can have a profound influence on their drinking behavior. Genetic and biological factors simply cannot account for the marked variation in rate of alcohol consumption that exists across cultures or for the diversity in drinking behavior that occurs temporally, geographically, and among social groups within a given culture.

The influence of sociocultural and contextual factors can be considered at three levels. Cultural or macrocontextual level influences refer to the effects of cultural norms and the manifestation of these normative standards in formal and informal regulatory practices that govern individual access to alcohol. The social level subsumes the influences of family, friends, and social institutions on individual drinking behavior and can include the effects associated with social modeling and social reinforcement. Microcontextual level influences include the specific social, physical, and temporal setting in which drinking takes place.

> *Cultural standards can become manifest in "formal" and "informal" responses to drinking, and such responses in turn can influence drinking behavior.*

Cultural or Macrocontextual Influences

Alcohol consumption and the standards that govern normal and pathological levels of drinking vary markedly across cultures (Bennett et al. 1993; Fillmore et al. 1993). Cultural standards can become manifest in "formal" and "informal" responses to drinking (i.e., normative influences), and such responses in turn can influence drinking behavior (Room 1991). Formal responses include the establishment of laws and sanctions that regulate access to and use of alcohol and the provision of treatment options aimed at remediating drinking problems (for a more comprehensive review of this area, see chapter 9). Informal responses include actions taken by family, friends, and acquaintances in attempting to control a drinker's behavior.

Normative influences can affect whether a population is viewed as wet or dry. For example, cultures can be defined as wet and dry depending on several characteristics, including drinking and abstention levels, attitudes about drinking, legal restrictions on alcohol, and traditions of temperance and prohibition (Hilton 1991). In a wet drinking culture (e.g., France and Italy), drinking is integrated into the social fabric of daily living (e.g., wine with meals), and access to alcohol is relatively high. In a dry drinking culture (e.g., Denmark and Sweden), drinking is episodic (e.g., binge drinking on weekends and holidays), and access to alcohol is restricted. Hilton (1991) applied the notion of wet and dry cultures to account for U.S. regional variation in drinking practices as determined in the 1984 National Alcohol Survey (Clark and Hilton 1991). "Wetter" regions (Northeast, Midwest, and Pacific) were characterized by relatively low levels of abstention and relatively favorable attitudes toward drinking and drunkenness. "Drier" regions (South and Mountain) were characterized by relatively high levels of abstention and relatively unfavorable attitudes toward drinking and drunkenness. Despite a relatively high rate of abstention, however, the per drinker rate of both alcohol consumption and problem drinking (the latter for males only) was higher within the drier than in the wetter regions of the United States.

Investigating acculturation patterns among immigrant populations is another approach for determining normative influences on drinking behavior (Heath 1993). Based on data from a collaborative Japan-U.S. study, Tsunoda et al. (1992) noted that the rate of heavy drinking among Japanese men was nearly three times greater than the rates among either Japanese-American or white men. Among Japanese women, the rate of abstention was nearly two times higher than among white women; abstention rates among Japanese-American women were intermediate. The marked gender difference in drinking practices observed among Japanese compared with Japanese-Americans may reflect differences in cultural norms governing the drinking of men and women. Kitano et al. (1992) reported that Japanese-American and Japanese men and women were equally likely to be intolerant of heavy drinking by adult women and any drinking by underage males and females. However, the belief that it was not wrong for a working-age man to get drunk was nearly five times more common among Japanese men and women than among Japanese-American men and women. Changes in cultural standards surrounding the propriety of male drunkenness appear then to have contributed to the reduced rates of heavy drinking observed among Japanese-American compared with Japanese men.

The effect of acculturation on drinking practices also has been explored in Hispanic cultures. In an analysis of drinking among a sample of U.S. Hispanics, Caetano (1987*a*) reported that those who are more acculturated to U.S. society drink more frequently in a number of social settings (e.g., bars, gatherings with friends, and club or organizational meetings). Acculturation also is associated with decreased abstention among older men and with a higher rate of frequent heavy drinking among younger men (Caetano 1987*b*). Women who are more acculturated to U.S. society have a fivefold increased chance of being frequent heavy drinkers than women who are considered to be less acculturated. Overall, the association between drinking patterns and acculturation is stronger and more consistent for women than for men.

Family and peers can influence drinking behavior actively, by explicitly encouraging or discouraging alcohol use, or passively, by providing models of drinking behavior.

Social Influences

Family and peer social influences have been extensively reviewed in earlier Special Reports; therefore, the discussion of these influences here will be brief. Family and peers can influence drinking behavior actively, by explicitly encouraging or discouraging alcohol use, or passively, by providing models of drinking behavior (Graham et al. 1991). In terms of social modeling, perceptions of how much peers drink may exert a stronger influence on an individual's drinking behavior than the actual level of peer drinking (for more discussion of this research, see chapter 9). College students, for example, consistently overestimate the degree to which their peers drink (Baer et al. 1991), and this cognitive bias may provide an excuse for heavy consumption or establish a cultural expectation that promotes heavy drinking (Baer and Carney 1993). Individuals also may model their drinking after someone they admire: Epstein et al. (1995) observed that among minority adolescents participating in the study, the drinking status of a person most admired by a study participant was related to the participant's drunkenness and future alcohol use.

As adolescents develop, drinking behavior becomes less influenced by parents and more influenced by peers. This transition between family and peer influence is perhaps best documented by considering how leaving home to attend college can affect a young adult's drinking behavior (Berkowitz and Perkins 1986). Parents can exert a moderating influence on the drinking behavior of their adolescent children by actively monitoring their alcohol use and by providing models of responsible drinking (Beck et al. 1991). Because college students living away from home are largely free from these parental restraints, it is therefore not surprising to find that they drink more heavily than students still living at home, especially if they are living in a setting such as a dorm or fraternity where there is likely to be a lot of encouragement and social modeling of drinking behavior (Barnes et al. 1992; Schall et al. 1992). Of interest is the observation that college students register less approval of heavy drinking during the spring term as compared with the fall term of their first year (Baer 1994); apparently, exposure to heavy-drinking peer models can moderate as well as promote alcohol use.

Microcontextual Influences

The social settings in which drinking takes place can influence drinking behavior. Observational studies of public drinking indicate that individuals are more likely to drink heavily when they are in a group, rather than when alone, and even more likely to drink heavily when the group contains at least one person who serves as a model for heavy drinking (Single 1993). The gender composition of drinking groups also can influence drinking behavior. Individuals in mixed-gender groups drink less than individuals in all-male groups (Hennessy and Saltz 1993; Sykes et al. 1993; Van De Goor et al. 1990), reflecting, perhaps, the effects of female disapproval on male drinking behavior (Connolly et al. 1992).

Drinking behavior also is influenced by physical and temporal context. Individuals drink more when they are released from daily routines on the weekends, during the holidays, and in the evening (Single 1993). The physical setting of a bar or tavern can influence individual level of consumption. For example, people tend to drink more in bars and taverns that provide televisions and games than those that do not provide these items, probably because the availability of these items lengthens the duration of the customers' stay (Single 1993). Moreover, individuals who consume a disproportionate amount of their total alcohol in bars and taverns are more likely to be heavy and problem drinkers than are individuals who consume a disproportionate amount of their alcohol at social gatherings (e.g., parties and weddings) (Single and Wortley 1993). Although these data do not resolve whether tavern going is a cause or consequence of heavy and problem drinking, they certainly highlight a potential focus for prevention efforts.

Stress

It is commonly believed that alcohol can relieve the psychological and physiologic sequelae of stress; thus, many people drink to control the experience of stress. The relationship between stress and alcohol, however, is complex (Sayette 1993). Although there is clear evidence that alcohol consumption is associated with stress, for at least some individuals at least some of the time, the relationship between stress and alcohol appears to be dependent on the nature of the stressor, the characteristics of the individual, and the context within which drinking occurs (Pohorecky 1991).

Observational studies of public drinking indicate that individuals are more likely to drink heavily when they are in a group, rather than when alone.

Stress can be conceptualized on three levels, the relevance of each of which has been explored in alcohol research. First, acute stressors refer to temporary but significant life changes that have generally transient effects. Alcohol research on acute stressors includes survey studies that explore the association between alcohol consumption and major life events (e.g., death of a spouse, natural disaster, or loss of one's job) and laboratory studies that examine the experimental induction of stress. Second, chronic stressors refer to enduring sources of irritation and distress that might be related to work (e.g., trouble with a coworker), family (e.g., concern about a child's ongoing academic troubles), or other life pursuits (e.g., living in a high-crime neighborhood). Third, traumatic stressors, such as childhood victimization or a prisoner of war experience, may be relatively delimited, yet the effects can be long lasting.

Effects of Chronic and Acute Stress

The relationship between exogenous stress and alcohol use is complex and is affected by the moderating influence of other factors, such as gender. Frone et al. (1994) found that stressful life events were more strongly associated with alcohol use in men than in women. In contrast, such events were associated with use of psychotherapeutic drugs (e.g., tranquilizers, barbiturates, amphetamines, and analgesics) in women. This study suggests that both men and women may try to relieve the stress response through use of pharmacologic substances, yet the preferred substance varies by gender.

The relationship between stress and alcohol consumption may vary across the life span. Although exposure to acute and chronic stress appears to be modestly associated with alcohol consumption among adolescents (DuBois et al. 1994; Wagner 1993), Welte and Mirand (1995) found no such relationship in a large representative sample of older adults. In addition, family factors may contribute to susceptibility to stress-induced drinking. Ohannessian and colleagues (1994) reported that a high level of chronic stress, as assessed by a daily hassles questionnaire, was associated with high levels of alcohol consumption for individuals having an alcoholic parent but not for individuals having no family history of alcoholism.

Experimental research has produced inconsistent findings on the stress-response-dampening effects of alcohol. Some studies have demonstrated an anxiolytic effect associated with alcohol, some studies have found no association, and some even have reported the opposite effect; that is, the induction of anxiety by alcohol (Sayette 1993). In a series of studies, Sayette et al. (Sayette and Wilson 1991; Sayette et al. 1992, 1994) have provided evidence suggesting that much of this inconsistency in findings may arise from the way that investigators have sequenced intoxication and stress induction. When exposure to the stressor precedes intoxication, the ingestion of alcohol tends to have little effect or may even produce anxiety. When intoxication precedes the induction of stress, however, alcohol ingestion tends to reduce anxiety. Sayette (1993) accounts for these findings by hypothesizing that the effect of alcohol on the stress response is mediated cognitively, by disrupting the appraisal of a stressful stimulus. Under this model, alcohol consumption attenuates the stress response when stress induction follows intoxication, by interfering with the individual's ability to fully appraise the nature of the stressor. Alternatively, alcohol consumption can heighten the stress response when stress induction precedes intoxication, by impairing the activation of coping strategies after exposure to a stressor that has been fully appraised while the individual was sober. The decision to drink in a naturally occurring situation, however, may depend more on a belief in, rather than the likelihood of, alcohol having an anxiolytic effect in that situation, a belief that would have been partially reinforced in the past.

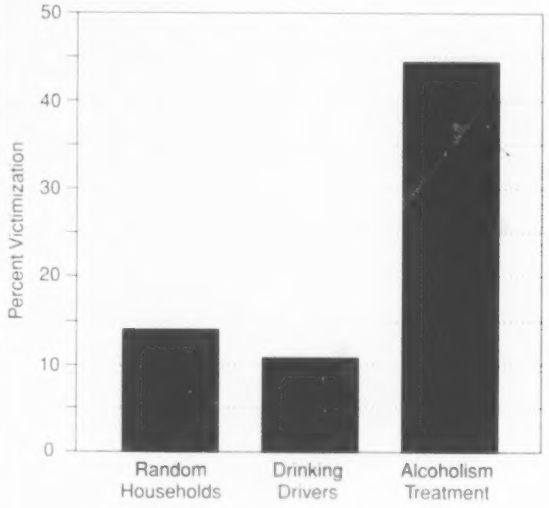
Traumatic Stressors: Effect of Childhood Victimization

Although clinicians have long suspected a link between childhood physical and sexual abuse and increased rates of alcohol and other drug abuse in adolescence and adulthood, researchers have only recently begun to explore systematically the significance of childhood victimization in the etiology of alcoholism. Miller et al. (1993) collected data through indepth interviews of 47 women between the ages of 18 and 45. The researchers reported that 45 percent of women seeking treatment for alcoholism said they had been abused both physically and sexually by their parents in childhood, compared with 11 percent of female first-time drinking and driving offenders and 14 percent of women identified through random-digit dialing (figure 5). Childhood victimization appeared to be associated specifically with alcohol problems, as the increased rate of childhood victimization among women in alcoholism treatment could not be attributed to demographic and background factors (e.g., parental alcohol problems). The reseachers also noted that the association was not due to an increased incidence of seeking help among victimized women, because the rate of reported abuse was significantly higher among women seeking treatment for alcoholism than among women seeking treatment for other mental health problems.

Wilsnack and Wilsnack (1995) also found that childhood sexual abuse is strongly associated with problem drinking in women within the general population. Findings from a 1991 survey showed that sexual abuse before age 18 was significantly related to problems associated with drinking, alcohol dependence symptoms, use of drugs other than alcohol, depression, anxiety, binge eating, and involvement in conflicted or violent relationships.

Figure 5. Self-reported rates of childhood victimization in three samples of adult women.

Figure gives the percentage of women in each sample who reported that they had experienced both severe violence and sexual abuse in childhood. Random household sample was derived using a random-digit dialing procedure (N = 82). Drinking and driving sample was obtained from classes for first-time drinking and driving offenders (N = 100). Alcoholism treatment sample was obtained from women seeking treatment at outpatient alcoholism clinics (N = 98).



Source: Miller et al. 1993. Reprinted with permission from *Journal of Studies on Alcohol*, Supplement No. 11, pp. 109–117, 1993. Copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, Piscataway, NJ 08855.

An association between childhood victimization and alcohol use disorders has also been observed in a consecutive series of 947 male and female inpatients admitted to a military medical center (Brown and Anderson 1991) and in a consecutive series of 189 women admitted to a psychiatric outpatient clinic (Swett et al. 1991). Although there is a need for prospective research in this area, findings from retrospective research clearly and consistently implicate early childhood victimization as an important influence on adult drinking problems, especially for women. Miller and Downs (1993) have speculated that the increased rate of alcohol problems among female victims of childhood abuse may be a result of lowered self-esteem, a hypothesis that is consistent with the observation that women who have been sexually abused have lower self-esteem than women who have not been sexually abused (Testa et al. 1992). Alternatively, Miller and Downs hypothesize that the experience of childhood sexual abuse can isolate young women from family and contemporaries and direct their affiliative tendencies toward deviant and delinquent peer groups in which heavy drinking is encouraged and valued.

Developmental Models

The research reviewed in this chapter indicates that multiple factors affect risk of alcoholism and that these factors do not act in isolation. For example, the protective physiologic effects of heightened alcohol sensitivity can be moderated by the cultural endorsement of heavy drinking. The effects of a family history of alcoholism can be tempered by the availability of support. Finally, the likelihood that stress exposure will lead to drinking can depend on the degree to which the individual is prone to experiencing psychological distress. One of the greatest challenges now facing alcohol researchers is integrating what is known about the multiple genetic, biological, psychological, and sociocultural determinants of alcohol use and abuse into realistic conceptual models that account for individual differences in drinking behavior.

An important advancement along these lines is the recognition that in many (perhaps all) cases, alcoholism is a developmental disorder.

An important advancement along these lines is the recognition that in many (perhaps all) cases, alcoholism is a developmental disorder. Common to the developmental models of alcoholism is the idea that the development of alcoholism is gradual, transpiring over the entire life span, and not abrupt, occurring only as a person crosses a diagnostic threshold (Zucker 1994). Accordingly, to fully understand the origins of alcoholism, researchers must begin by studying young children at an age when they are learning and developing attitudes about alcohol (e.g., Fitzgerald et al. 1993). These children should be followed through adolescence, when they initiate their use of alcohol, and through adulthood, when stable patterns of alcohol use or abuse are established. Developmental models also recognize that the course of development is characterized by a dynamic interplay between the organism and its context; the individual adapts to contextual changes but also plays a large role in driving the nature of his or her experiences (Zucker 1994). Thus, research on the origins of alcoholism has to investigate the reciprocal interactions among biological, psychological, and sociocultural influences.

The developmental approach to alcoholism can be illustrated by briefly describing a specific model, namely the vulnerability model, which is based on and extends research reviewed in earlier sections of the chapter. More detailed discussion of developmental approaches to alcohol use and abuse can be found in the work of Zucker and Fitzgerald (1991), Zucker et al. (1994), and Petraitis et al. (1995).

Sher (1991) and Tarter and Vanyukov (1994) have proposed vulnerability models that consider the simultaneous influence of multiple biological and sociocultural factors in the development of alcoholism. A central element of these models is the notion that an inherited vulnerability, transmitted from one generation to the next, is necessary although not sufficient for the development of alcoholism. Inherited vulnerability is conceptualized as multifaceted and includes factors such as a "difficult temperament," impaired cognitive functioning, and altered sensitivity to alcohol's effects; such factors differentiate the offspring of alcoholics from the offspring of nonalcoholics. An inherited vulnerability, however, only establishes a level of risk. The likelihood that this risk is ever manifested as alcoholism will depend on the degree of environmental provocation. As compared with individuals who did not inherit high standing on the risk factors associated with alcoholism, individuals who are vulnerable are more likely to both experience and be influenced by circumstances that increase the likelihood they will develop drinking problems.

Given the multidimensional nature of vulnerability and its environmental influences, vulnerability models subsume a multiplicity of developmental pathways that end in alcoholism. Sher (1994), for example, describes three distinct pathways: enhanced reinforcement, deviance proneness, and negative affect. A brief description of the deviance proneness pathway serves to illustrate the conceptual nature of these models. Because the offspring of alcoholics are more likely than offspring of nonalcoholics to be impulsive, inattentive, and hostile, they also will be more difficult to socialize than children who are controlled, attentive, and agreeable. Moreover, the offspring of alcoholics are more likely to be reared in homes marked by conflict and ineffective parenting. The inheritance of a difficult temperament in combination with ineffective parenting is likely to lead to socialization deficits, academic failure, and affiliation with deviant peer groups in which alcohol use and abuse is modeled and reinforced. If these offspring persist in this pattern, they are likely to develop chronic alcohol abuse.

Summary

Current research on the determinants of drinking and alcoholism range from molecular studies to research on integrative, developmental models. Some alcohol researchers are using molecular genetic techniques to search for the specific genes that contribute to alcoholism risk. Others are taking advantage of recent developments in the cognitive sciences to develop models of how alcohol memories are stored. Other researchers still are using qualitative research methods to determine how alcohol is viewed in a specific culture. Despite the multiplicity of approaches and conceptual orientations, several general trends can be noted.

Drinking behavior and alcoholism are complex human behaviors that admit a diversity of underlying causes. Genetic factors clearly play a role in the etiology of alcoholism, and alcohol researchers are now well positioned to identify the specific genes that affect risk for alcoholism and to determine the biochemical and neurophysiologic consequences of those gene effects. Important progress has already been made in identifying the effects of alcohol metabolizing genes and showing how those genes influence drinking behavior among certain Asian populations. Animal models of alcoholism are proving to be instrumental in identifying potential genetic factors that confer vulnerability to alcoholism in humans. Researchers are using QTL analysis in mice to identify possible locations of genes that influence alcohol-related behaviors. For example, scientists recently identified two loci—*Alcp1* and *Alcp2*—that appear to have significant gender-specific effects on alcohol consumption in mice.

Significant progress also has been made in understanding the role of alcohol sensitivity in drinking behavior. The offspring of alcoholics do inherit altered sensitivity to alcohol's effects, and this altered sensitivity appears to be a good predictor of who does and does not go on to develop alcoholism.

Psychological factors also clearly play a role in the etiology of alcoholism and drinking behavior. The personality dimensions of behavioral undercontrol and negative emotionality differentiate, on average, those who will go on to develop alcohol problems from those who will not. Cognitive psychologists have shown that individuals who are heavy drinkers have different expectations about the effects of alcohol and store these expectations differently in memory than those who are light drinkers. Rather than being a simple consequence of an individual's drinking history, these cognitions and the manner in which they are stored appear to be powerful motivators of drinking behavior.

Sociocultural and contextual factors also influence drinking behavior. Cultural norms influence individual attitudes about the propriety of drinking, and these attitudes affect whether, how much, and when a person drinks. Drinking behavior is influenced by friends' drinking behaviors, parental standards regarding drinking, and the extent to which a person has been exposed to or is experiencing severe psychological stress.

Rather than being viewed as in competition with one another, these multiple influences can be usefully conceptualized as falling along a pathway that links molecular studies to developmental studies which address the confluence of the many factors involved in the development of alcoholism. Genes control the synthesis of proteins that influence biochemical systems and neurophysiologic processes. In turn, these elements affect personality dispositions and cognitive functioning, and so on. Moreover, these biological pathways are not closed but rather are constantly modulated by external factors. Ample research now indicates that biological and nonbiological factors both influence drinking behavior and that the two types of influences are interdependent. For example, even though we can safely predict that an individual inheriting ALDH2 deficiency will be much less likely to develop alcoholism than an individual not inheriting the enzyme deficiency, precise prediction of outcome will require additional knowledge of that individual's cultural context and alcohol-specific expectancies.

Ultimately, the purpose of etiologic research is to inform prevention and intervention efforts. Alcohol researchers are working toward achieving this goal by developing integrative models that simultaneously consider the multiple factors that influence drinking behavior and how those influences unfold over an individual's life span.

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Chapter 3

Actions of Alcohol on the Brain

Introduction

The mechanisms by which alcohol produces intoxication, reinforcement of continued drinking, dependence, and withdrawal upon cessation of drinking are based chiefly in the brain. Recent progress in neuroscience research has yielded information critical to characterizing the cellular and molecular processes that occur in the central nervous system (CNS) in response to alcohol and has helped associate these processes with the behavioral and physiologic manifestations of alcohol use and abuse.

Technological advances in physiology, biochemistry, genetics, and molecular biology have equipped neuroscientists with powerful tools for the study of alcoholism. These tools include sophisticated methods for examining the functions of nerve cells and molecules in both cultured cells or tissues (in vitro) and animal models (in vivo). New techniques in molecular biology have allowed genes that are potential targets of alcohol to be isolated and expressed as fully functional proteins in cells such as *Xenopus* oocytes (frog eggs), enabling researchers to examine alcohol's effects on these proteins in a well-characterized, easily manipulated environment. Manipulations involving the mutation or deletion of portions of alcohol-sensitive genes permit in vitro or in vivo characterization of particular alcohol-sensitive regions of proteins corresponding to those genes. Advances in genetics have led to the creation of animal models that allow direct testing of alcohol's effects on the expression and function of genes and proteins in intact animals.

These and other experimental approaches have identified numerous mechanisms by which acute and chronic alcohol exposure affect *neurotransmitter*[1] function and other cellular activities to influence brain chemistry and behavior. Such findings have helped to explain the brain processes that lead to alcohol dependence and abuse and also suggest molecular targets for pharmacologic treatments that may prevent or attenuate alcoholism and its harmful consequences. This chapter first provides an overview of the normal molecular and cellular events that regulate CNS activities, as background for considering alcohol's disruption of brain function. Following is a review of current research describing the many nerve cell molecules and functions altered by acute and chronic alcohol exposure and the consequences of these alterations.

Cellular and Molecular Aspects of Brain Function

Cells of the Brain

The signaling and information-processing functions of the brain are accomplished primarily by neurons, or nerve cells. Approximately 1 trillion neurons provide the capacity for sensation, movement, language, thought, and emotion. Neurons in different brain regions vary in size, shape, and electrical properties, but most share certain features: a cell body containing a nucleus, which holds the cells' genetic information; tree-like networks of dendrites, which integrate information from other neurons; and a single axon, which passes from the cell body to contact dendritic trees of other neurons (figure 1). The end of the axon branches into a network of axon terminals that are separated from adjacent dendrites by a microscopic gap called a *synapse*. Presynaptic axon terminals release neurotransmitters in response to stimuli; postsynaptic dendritic terminals receive and

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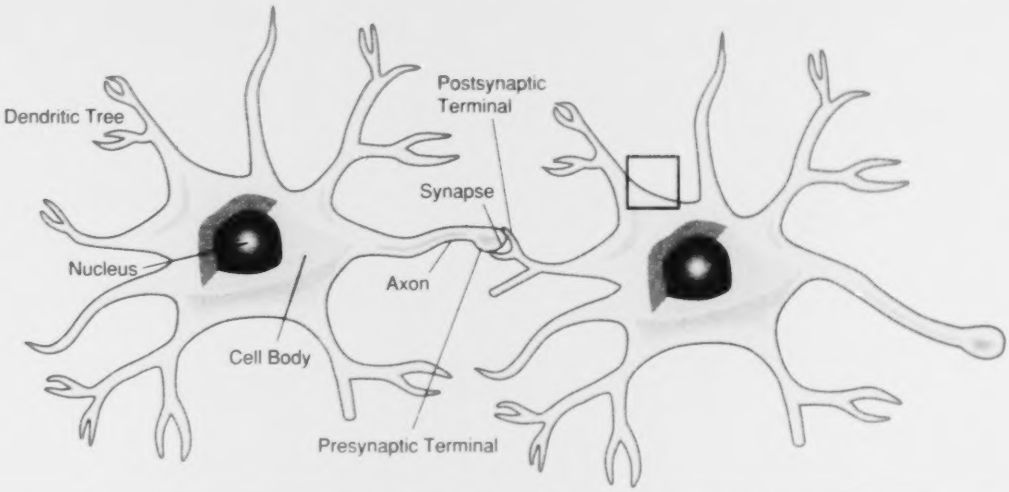
[1] For a definition of *neurotransmitter* and other terms in this chapter, see the glossary.

Figure 1. Structural features of a presynaptic and postsynaptic neuron.

This schematic drawing depicts the major components of neuronal structure, including the cell body, nucleus, dendritic trees, and synaptic connections. The box encloses a region of the neuron cell membrane that is enlarged in figure 2.



respond to these neurotransmitters. Each neuron forms synapses with many (up to 1,000) other neurons and, in turn, receives synaptic connections from an equally large number of neurons. Interspersed among neurons are glial cells, which provide neurons with an insulating layer of *myelin* to enhance the transmission of nerve impulses.

Cellular Compartmentalization and Organization of Nerve Cell Activities

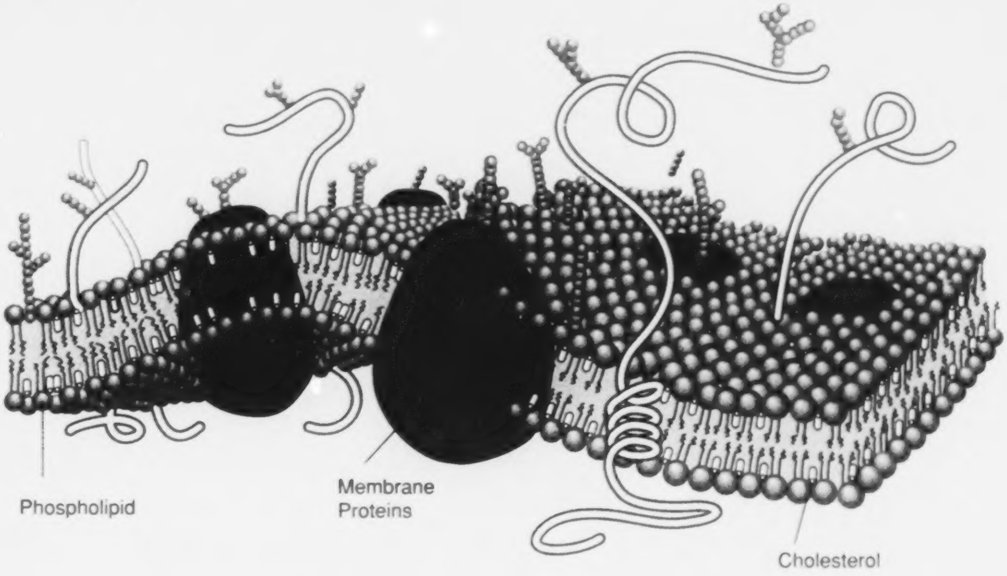
The cellular activities critical to normal CNS function take place in specialized compartments and membrane structures of the neuron, including the nucleus, the cytoplasm, and the cell membrane. Housed in the nucleus are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA, specifically messenger RNA, or mRNA), molecules that encode and direct the synthesis of cellular proteins via processes of *transcription* and *translation*. During gene transcription, the genetic code of DNA is converted into complementary strands of mRNA. Next, segments of this mRNA are deleted and the strand is spliced, a process that may yield mRNA encoding different forms, or splice variants of the same protein. The modified mRNA is transported from the nucleus to the cytoplasm, a solution of salts containing the *enzymes* and specialized structures (organelles) that assist in protein synthesis and other cellular metabolic events. Here, mRNA molecules are translated into a chain of amino acids that form the protein, which is then inserted into the cell membrane or transported to other sites of action within or outside of the cell.

The cell membrane helps to provide structural integrity to the neuron, serves as a barrier to water-soluble molecules, and contains proteins that regulate intracellular responses to changes in the external environment. This membrane is a fluid double layer, or bilayer, consisting primarily of phosphate- and sugar-containing fatty compounds (phospholipids and glycolipids, respectively) and cholesterol (figure 2). Phospholipids and glycolipids are arranged with their fatty acid chains within the membrane core and their charged head groups facing the cytoplasm or the extracellular space. Proteins embedded in the fatty bilayer include *ion channels*, neurotransmitter *receptors*, coupling proteins (G proteins), and enzymes; the functions of these membrane proteins are detailed later.

The close relationship between lipids and proteins in the bilayer suggests that the normal function of these proteins may depend on the presence of lipids. The chemical and structural nature of the cell membrane render it readily permeable to alcohol. Thus, alcohol has access to and may directly perturb the function of signaling proteins outside the cell, in the cell membrane, or within the cell. Alcohol also may alter the fluid

Figure 2. The cell membrane (enlarged from figure 1).

The membrane is composed of various lipids arranged in a bilayer. Cholesterol and proteins are embedded in this bilayer. Membrane proteins help receive and transmit information in the form of signal molecules, such as ions or neurotransmitters, that regulate cell functions.



Source: Adapted from Bretscher 1985. Adapted from The molecules of the cell membrane, Bretscher, M.S. Copyright © 1985 by SCIENTIFIC AMERICAN, INC. All rights reserved.

character of the fatty bilayer, with indirect effects on membrane protein functions.

Neuronal Transmission of Information

Information moves across a neuron as a wave of electrical impulses that travels from the cell's dendritic region to its axon terminal. The ability to generate this traveling nerve impulse, or action potential, is unique to neurons. The generation of nerve impulses is regulated by ion channels and ion pumps that control the transmembrane flow of electrically charged molecules, such as sodium, potassium, calcium, and chloride, and help to maintain resting conditions within the neuron.

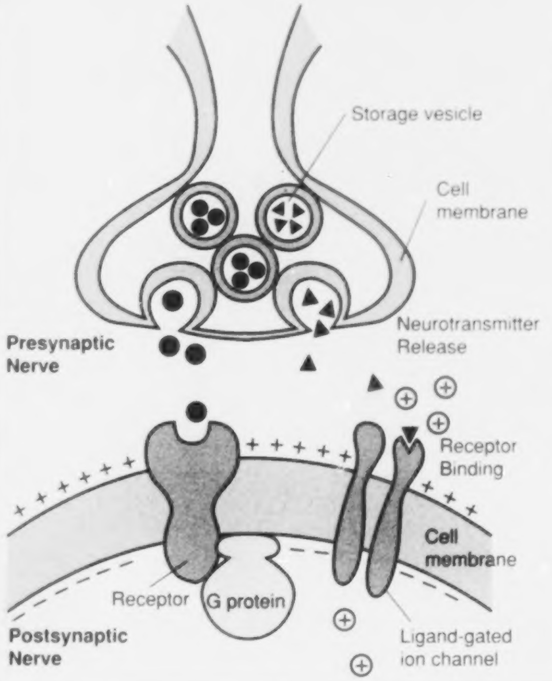
In the absence of stimulation, ion concentrations on either side of the neuronal membrane create a resting charge differential. Signals received by dendrites can disrupt this charge differential to produce a nerve impulse. Typically, an impulse is generated when specialized membrane ion channels open briefly in response to neurotransmitters or changes in voltage, allowing the entry or exit of ions. The result is *depolarization*, or a reduction in the membrane's charge differential. If the signal is strong enough, a wave of membrane depolarization travels the length of the neuron until it reaches the axon terminal.

The arrival of a nerve impulse at the presynaptic terminal opens specialized calcium channels. Calcium ions then flow into the cell, causing intracellular storage vesicles that contain neurotransmitters to move to the cell membrane and release their contents into the synaptic cleft (figure 3). The neurotransmitters diffuse across the synapse to adjacent dendrites of postsynaptic nerve cells, inducing changes in the electrical or chemical properties of postsynaptic membranes. Neurotransmitter activity ends when neurotransmitters diffuse away from the synapse or when they are metabolized or taken up by presynaptic terminals.

Neurotransmitters may either excite or inhibit postsynaptic neurons. Excitatory neurotransmitters allow positively charged ions to enter the neuron, causing an excitatory depolarization of the postsynaptic membrane. Inhibitory neurotransmitters allow negatively charged ions to enter the neuron, increasing the electrical charge across the postsynaptic membrane and reducing excitability. Excitatory and inhibitory stimuli may act together to exert additive or canceling effects on the postsynaptic neuron. In this way, the dendritic tree of a single neuron may respond to the simultaneous activity of many adjacent neurons.

Figure 3. Synaptic transmission—a schematic view of the presynaptic nerve terminal and the postsynaptic membrane.

Neurotransmitters are released from the presynaptic nerve terminal when the arrival of a traveling nerve impulse causes storage vesicles to fuse with the presynaptic membrane. Neurotransmitters diffuse across the synapse and bind to receptors or ligand-gated ion channels in the postsynaptic membrane. Binding of neurotransmitters to some neurotransmitter receptors activates G proteins, which in turn initiate reactions that produce intracellular functional changes and may directly influence the activity of ion channels. Binding of neurotransmitters to ligand-gated ion channels alters the structure of the channel to allow the entry or exit of positively or negatively charged ions, which in turn reduces the electrical charge differential across the membrane.



Transmembrane Signaling

Alcohol's most prominent effects on nerve cell function involve alterations in synaptic transmission (Weight 1992). For this reason, researchers have focused on understanding how alcohol disrupts the many signaling processes that govern synaptic transmission.

Different neurotransmitters are recognized by specific receptors embedded in the neuronal membranes. The shape of a given receptor confers specificity for a particular neurotransmitter. Binding by the appropriate neurotransmitter produces a change in receptor shape that triggers the activity of other proteins in the membrane and, ultimately, within the cell.

Some neurotransmitter receptors are specialized ion channels, known as ligand-gated ion channels. The receptor for the neurotransmitter acetylcholine is an example. When acetylcholine binds to its receptor, the receptor changes shape to allow influx of sodium ions; in turn, these ions cause membrane depolarization (Unwin 1995). Gamma-aminobutyric acid (GABA), the brain's major inhibitory neurotransmitter, and glutamate, the brain's major excitatory neurotransmitter, also act through ligand-gated ion channels. When GABA binds to its receptor, negatively charged chloride ions enter the nerve cell and cause a reduction in neuronal excitability. Glutamate acts through a different receptor complex, causing positively charged ions to flow into the cell; in turn, this movement of ions depolarizes the neuronal membrane, opens sodium channels, and ultimately leads to the firing of a nerve impulse.

Some neurotransmitter receptors are coupled to G proteins; that is, proteins with activities that are regulated by binding to the high-energy compound guanosine triphosphate (GTP). G protein-linked receptors typically influence neuron function through indirect effects on ion channels or neurotransmitter release. Binding of neurotransmitters to these receptors induces G-protein activity, which may directly influence the activity of ion channels (Hille 1994). Alternatively, G proteins have indirect effects on ion channel activity through the generation of *second messengers*. One group of G protein-linked receptors controls the activity of adenylate cyclase and guanylate cyclase, enzymes that produce the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), respectively. Another group of G protein-linked receptors controls the activity of phospholipase C, an enzyme that regulates the release of the second messengers inositol triphosphate and diacylglycerol.

Intracellular changes in second messenger levels modify the electrical excitability and chemical properties of postsynaptic neurons. Inositol triphosphate acts to increase the intracellular concentration of calcium. Diacylglycerol and cAMP regulate the activity of protein kinases, enzymes that *phosphorylate*, or add charged phosphate groups to, specific cellular proteins. *Phosphorylation* by protein kinases regulates the activity of various ion channels, receptors, G proteins, and enzymes as well as the transcription of DNA and the synthesis of cellular proteins, with diverse and potentially profound consequences for neuron function.

Actions of Alcohol on the Central Nervous System

Although alcohol ingestion initially induces a pleasurable state of mind, excessive drinking leads to confusion, incoordination, sedation, and sometimes coma (Charness et al. 1989). Alcohol has known reinforcing effects that may explain why some people seek repeated exposure to alcohol despite these and other adverse consequences. Prolonged drinking results in tolerance to alcohol's effects and may lead to craving for alcohol and to physical dependence. In alcohol-dependent individuals, cessation of drinking produces symptoms of withdrawal, such as tremors, hallucinations, and seizures. A fundamental challenge to alcohol researchers is to understand the brain structures and CNS activities involved in intoxication, reinforcement, tolerance, and dependence.

Alcoholic blackouts likely represent disruption of function in the hippocampus, a structure critical to consolidating new memories.

Intoxication

Consumption of alcohol leads to a dose-dependent, transient elevation of blood alcohol concentration (BAC). In an inexperienced drinker, low BACs (25–45 milligrams/deciliter [mg/dL], or one to two drinks[2] containing one-half of an ounce of ethyl alcohol) produce increased sociability, euphoria, and mild motor incoordination. BACs of 80–100 mg/dL correspond to legal limits set by States to enforce safe driving and are associated with changes in gait, concentration, and reaction time. Episodes of short-term amnesia (alcoholic blackouts) may occur with BACs at and above 80 mg/dL. BACs of 100–150 mg/dL can produce more overt signs of intoxication, including gait ataxia (inability to walk straight), nystagmus (rhythmic movements of the eyes), impaired mental and motor skills, sedation, and confusion. In nonalcoholic individuals, BACs above 400–500 mg/dL are commonly fatal.

Behavioral and physiologic changes observed with intoxication reflect effects of alcohol in various structures and functions of the brain. Motor incoordination observed in intoxicated individuals may result from actions of alcohol in the cerebellum, which participates in the control of movement. Alcohol has been shown to suppress nerve impulses released by Purkinje cells, cerebellar neurons that send sensory and movement-related messages to various parts of the body (Weight 1992). The euphoric and anxiolytic (anxiety-reducing) effects of alcohol may be mediated by networks of nerve cells in various brain regions that subserve emotion, including the *hypothalamus, septal area, amygdala, ventral tegmental area, nucleus accumbens,* and *cingulate gyrus.* Sedation, confusion, and impaired cognition suggest widespread effects of alcohol on the cerebral cortex, which controls higher mental functions, perception, and behavioral reactions, and its functionally related structures in the *pons.* In addition, the sedative hypnotic properties of alcohol result in part from the drug's ability to enhance the inhibitory effects of GABA and inhibit the excitatory actions of glutamate (Weight 1992). Alcoholic blackouts likely represent disruption of function in the *hippocampus*, a structure critical to consolidating new memories. Death after excessive drinking results from suppression of brain stem activities that control respiration (Charness 1989; Charness et al. 1989).

Reinforcement

Alcohol's reinforcing properties are those that increase the likelihood of future alcohol consumption, a behavior thought to contribute to the development of chronic drinking, dependence, and craving. Alcohol may have positive reinforcing effects, as exemplified by its pleasant

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[2] BACs produced by any given number of drinks differ according to various factors, including a person's genetic makeup, weight, lean body mass, gender, age, health, and the rate of alcohol intake.

Glossary

Affinity—A measure of the strength with which a molecule, such as a *neurotransmitter* or alcohol, binds to another molecule or cell structure, such as a *receptor* or membrane.

Agonist—An agent that mimics the actions or effects of another agent (e.g., a drug that mimics the effects of a *neurotransmitter*).

Amygdala—An almond-shaped structure found within the tip of the temporal lobe of the brain. The amygdala has connections to the *hippocampus, septal area, thalamus,* and *hypothalamus.*

Antagonist—An agent that blocks or reverses the actions or effects of another agent (e.g., a drug that blocks the effects of a *neurotransmitter*).

Autonomic—Pertaining to the autonomic nervous system, or that portion of the nervous system concerned with regulating the activity of smooth muscle, cardiac muscle, and glands.

Cingulate gyrus—An arch-shaped structure closely aligned with the surface of the corpus callosum, which is the bundle of fibers that connect the brain's two hemispheres.

Clone—A process in which a gene is isolated and duplicated in cultured cells, or the cell containing such a gene. Cloning allows scientists to make many copies of a gene of interest.

Depolarization—A process by which the electrical gradient along the cell membrane is altered, causing a reduction in the electrical charge differential across the membrane.

Dopaminergic—Relating to neurons or nerve fibers that respond to dopamine.

Endorphins—Small *neuropeptides* that bind to opiate receptors in the brain and have strong analgesic activity.

Enkephalins—Small *neuropeptides* that bind to opiate receptors in many locations in the brain and spinal cord and participate in the regulation of movement, mood, behavior, neuroendocrine regulation, and perception of pain.

Enzyme—A highly specialized protein that catalyzes a specific chemical reaction.

Excitotoxicity—The process by which excessive influx of calcium into the cell leads to cell death.

Germ cells—Cells from which gametes, or eggs and sperm, are derived.

Granule cells—Tiny, star-shaped neurons found in the granular layers of the cerebral and cerebellar cortices.

Heat shock protein—A protein made by the cell in response to stress such as elevated temperatures or chemical exposure. Heat shock proteins are thought to have repair roles (e.g., they may refold denatured or misfolded proteins).

Hippocampus—A curved ridge found within the cerebral hemisphere that functions in consolidation of new memories.

Hydrophobic—Describes chemical groups or compounds, such as lipids, that are insoluble in water.

Hyperpolarization—A process by which the electrical gradient along the cell membrane is altered (i.e., an increase in the electrical charge difference across the membrane).

Hypothalamus—A region of the brain that is involved in basic behavioral and physiologic functions. These functions are critical to the maintenance of the internal environment in response to stress and other stimuli and are implicated in hunger, thirst, and heightened emotional drives.

Ion channels—Proteins that span the cell membrane, forming pores that regulate the flow of specific charged particles into and out of the cell.

Ions—Small, electrically charged molecules.

Isoform—Multiple forms of the same molecule, typically a protein or enzyme.

Locus coeruleus—A pigmented eminence in the base of the brain that plays a role in vigilance reactions and arousal to sensory stimuli.

Membrane potential—The difference in electrical charge across the cell membrane.

Myelin—A substance found in the membrane of Schwann's cells, a type of glial cell that wraps the axons of peripheral neurons. Myelin acts as an electrical insulator.

Neuropeptides—Molecules composed of short chains of amino acids found in brain tissues. Neuropeptides are thought to act as *neurotransmitters* and include *endorphins* and *enkephalins.*

Neurotransmitter—A chemical messenger released by an excited or stimulated nerve cell. After being released, neurotransmitters travel across a synapse and then bind to a receptor on an adjacent nerve cell, usually triggering a series of chemical and electrical changes in the second cell.

Neurotrophin—A factor that promotes the survival, growth, and differentiation of selected neuronal populations.

Nucleus accumbens—A brain structure affected by many drugs of abuse and implicated in the rewarding properties of addictive drugs.

Opioid—Any of a group of peptides, such as *endorphins* and *enkephalins,* that bind to or otherwise influence opiate receptors in the brain.

Phosphorylation—A chemical reaction resulting in the formation of a phosphate derivative of a molecule. Phosphorylation reactions are often critical to regulation of receptor activity and the functions of other proteins.

Pons—A broad mass of nerve fibers that forms the central portion of the brain stem. The pons participates in control of respiration and coordination of muscular activity.

Potentiate—To make more effective or active.

Receptor—A complex protein structure that recognizes and binds *neurotransmitters* or interacts with specific *enzymes.*

Recombinant—Relating to genetically engineered deoxyribonucleic acid (DNA) prepared in vitro by cutting DNA molecules into fragments and splicing these fragments together.

Second messenger—A signaling molecule that participates in the intracellular reactions resulting when a stimulus, such as a *neurotransmitter,* binds to a *receptor.*

Septal area—A region stretching as a thin sheet within the cerebral hemisphere that has functional connections with the *hypothalamus* and the *hippocampus.*

Striatum—A mass of gray and white substance positioned in front of the *thalamus* in each cerebral hemisphere of the brain.

Synapse—The site of communication between neurons.

Thalamus—A brain region that serves as a communication center which relays information to the cerebral cortex.

Transcription—The process by which a portion of DNA that is coded for a specific protein is converted to messenger RNA (mRNA). This process takes place in the nucleus of the cell.

Transduce—To convert energy or a message to another form, as when a *neurotransmitter* binds to a nerve cell *receptor* and thereby initiates biochemical reactions and functional changes within the cell.

Translation—The process by which mRNA is converted into a protein or a smaller, protein-like substance known as a polypeptide. This process occurs outside the nucleus at a cellular structure called the ribosome.

Upregulate—To increase the activity or level of a protein, such as a *receptor.*

Ventral tegmental area—The midbrain region containing dopamine cell bodies that project to the *nucleus accumbens.*

euphoric actions, or negative reinforcing effects, as exemplified by its anxiolytic properties.

Researchers are exploring the neuropharmacologic effects that reinforce alcohol-seeking behavior and the specific brain pathways involved. Brain regions implicated in alcohol reinforcement include areas of the hypothalamus associated with thirst, hunger, and heightened emotional drives (Lewis and Lockmuller 1990). Key neurotransmitters that appear to play a role in alcohol's reinforcing effects include GABA, dopamine, and serotonin (5-hydroxytryptamine, or 5-HT).

Tolerance

Tolerance is a general term applied to compensatory adaptations. The brain and body adapt to chronic alcohol exposure. As a result, higher BACs are required to produce a state of intoxication, and BACs that would prove lethal in people who are not alcoholics may produce no discernible intoxication in alcoholics. For example, alcoholics who have developed tolerance appear to remain sober even at BACs of 230–460 mg/dL and can survive with BACS that exceed 1,000 mg/dL (Charness et al. 1989). Because more alcohol is required to achieve the same effect and because higher BACs are maintained for longer periods of time, the development of tolerance allows and may encourage increased alcohol intake and contributes to alcohol-induced organ damage, including damage to the brain.

> *Chronic alcohol exposure can result in not only tolerance to alcohol's effects but also a requirement for the presence of the drug for normal nerve function.*

Metabolic, behavioral, and neuronal mechanisms contribute to the development of tolerance. Chronic alcohol consumption increases levels of liver enzymes that metabolize alcohol, effectively increasing the ability of the liver to break down alcohol so that a larger dose is needed to achieve the same blood and brain alcohol levels. Behavioral tolerance describes the learned ability of a person or laboratory animal to function under the influence of alcohol or other drugs. Behavioral manifestations of tolerance are thought to involve adaptive, or plastic, CNS processes similar to learning and memory. Underlying these behavioral changes may be alcohol-induced changes in neuronal function. Chronic alcohol exposure can produce adaptive responses in neurons and can result in not only tolerance to alcohol's effects but also a requirement for the presence of the drug for normal nerve function. These adaptive responses appear to involve alterations to neural cell membranes, functions of ion channels, and responses to neurotransmitters such as GABA and glutamate.

Physical Dependence and Withdrawal

In addition to tolerance, chronic alcohol consumption may result in physical dependence, a state in which alcohol is required to maintain normal CNS function (Charness et al. 1989). Like tolerance, physical dependence involves adaptive changes in CNS activities. In alcohol-dependent persons, cessation of drinking may lead to craving for alcohol and symptoms of alcohol withdrawal syndrome. Withdrawal symptoms develop because adaptive changes that render CNS function normal in the presence of alcohol become maladaptive when alcohol intake is abruptly discontinued.

Symptoms of alcohol withdrawal include tremulousness, agitation, and *autonomic* hyperactivity (characterized by sweating, increased blood pressure, and rapid heart rate) that contrast sharply with the sedative effects typical of acute intoxication (Charness et al. 1989). Alcohol withdrawal syndrome evolves gradually over hours to days after the cessation of drinking. Tremulousness appears after 8–12 hours, followed in some instances by generalized seizures. Delirium tremens, a state of autonomic hyperactivity, agitation, and hallucinations, typically begins within 2 days after alcohol withdrawal and may last several days, a week, or more.

The cellular and molecular mechanisms responsible for these adaptive CNS responses, as well those involved in the intoxicating and reinforcing properties of alcohol, are areas of active investigation. Neuroscientists have begun to understand responses to alcohol in terms of its long- and short-term impact on nerve cell membranes; functions of neurotransmitters, their receptors, and related intracellular signaling molecules; and intracellular activities such as gene expression.

Alcohol and Cell Membranes

Alcohol typically produces intoxication at concentrations of approximately 80 mg/dL—about 10 million times higher than the intoxicating concentrations of opiates (Charness 1990). At these high concentrations, alcohol changes the physical properties of neural membranes and disrupts the function of a selective number of proteins, such as receptors and ion channels, involved in synaptic transmission. Alcohol differs from other psychotropic drugs in that it does not act through a specific membrane receptor but rather affects the functions of many different membrane proteins. Whether alcohol's effects arise from its disruption of membrane lipids or result from direct effects on membrane proteins remains unclear (Wood and Schroeder 1992).

Alcohol does not act through a specific membrane receptor but rather affects the functions of many different membrane proteins.

Initial theories postulated that alcohol and general anesthetics act by permeating the membrane and disordering membrane lipids, thereby changing the shape, interactions, and function of membrane proteins (Deitrich et al. 1989; Weight 1992). Studies using probes for specific membrane regions (Wood et al. 1991) show that alcohol alters membrane fluidity and protein distribution in these regions and that its actions are greater in membranes isolated from rat strains that are sensitive to alcohol's effects compared with their alcohol-insensitive counterparts (Avdulov et al. 1994; Schroeder et al. 1994).

Overall, alcohol appears to have an asymmetric effect on the interior and exterior portions (domains) of the cell membrane: The drug appears to disorder, or fluidize, the interior domain and order the surface domain of synaptic membranes (Colles et al. 1995; Wood and Schroeder 1992). Alcohol's effects on membrane structure vary with concentration. At low concentrations, alcohol has a greater *affinity* for the interior domain, whereas at high concentrations, alcohol partitions preferentially in the surface domain (Colles et al. 1995; Hitzeman et al. 1986; Wood and Schroeder 1992). Alcohol treatment also may produce electrical changes in both interior and exterior domains of synaptic membranes (Colles et al. 1995).

Recent studies have provided evidence for a direct effect of alcohol on membrane proteins. Alcohol treatment can alter functions of ligand-gated ion channels, and data from pharmacologic studies of several different ligand-gated ion channels suggest that alcohol binds directly to a distinct binding pocket on each receptor protein (Li et al. 1994; Peoples and Weight 1995). A direct suppressive effect of alcohol on the activity of lipid-free protein kinase C (PKC), an enzyme critical for many intracellular functions, also has been reported (Slater et al. 1993). However, Slater et al. suggest that alcohol-induced alterations to membrane lipids also may influence PKC function, possibly by affecting the shape of the protein. Thus, alcohol may alter neuronal function through effects on both membrane lipids and membrane proteins. The following paragraphs focus on various neuronal cell membrane proteins and the impact of acute and chronic alcohol exposure on their function.

Neurotransmitter Release and Receptor Activation

The diverse behavioral effects of alcohol presumably reflect its diverse activities in multiple neurotransmitter systems. Alcohol can alter the functioning of neurotransmitters, neurotransmitter receptors, or both. Alcohol can stimulate the release of neurotransmitters and can augment or antagonize functions of neurotransmitter receptors, as detailed below.

Dopamine

Alcohol can influence the release of dopamine, a neurotransmitter of particular importance in addiction. Dopamine is thought to mediate the pleasurable sensations associated with eating, drinking, sex, and other strongly motivated behaviors and has been implicated in the positive reinforcing effects of alcohol (Di Chiara and Imperato 1988; Koob 1992). Dopamine-containing neurons of the ventral tegmental area extend into the nucleus accumbens, a brain structure affected by many drugs of abuse and implicated in the rewarding properties of addictive drugs (Di Chiara and Imperato 1988). Studies in animals have shown that the firing of nerve impulses by ventral tegmental neurons and the release of dopamine in the nucleus accumbens increase during acute alcohol exposure (Brodie et al. 1990; Weiss et al. 1993) and decrease markedly during alcohol withdrawal (Diana et al. 1992*b*, 1993). Other animal studies show that long-term alcohol exposure does not produce tolerance to alcohol-induced increases in ventral tegmental firing and dopamine release (Diana et al. 1992*a*). These findings suggest that tolerance does not develop to alcohol's rewarding effects and that dopamine neurotransmission may therefore contribute to the reinforcing properties of alcohol. With alcohol withdrawal, reductions in *dopaminergic* activity are observed that may contribute to development of aversive withdrawal symptoms and thus to the maintenance of abusive drinking (Diana et al. 1992*b*).

Alcohol-stimulated dopamine release can be prevented by different drugs. Some of these drugs act as *antagonists*, or substances that block or reverse the effects of another substance. Many of the antagonists that block dopamine release have proven potential for reducing craving for alcohol. Among these drugs are antagonists of *opioid* peptides, such as *enkephalins* and *endorphins*, which are released in the brain to produce euphoric effects in response to alcohol or other drugs (Acquas et al. 1993; Devoto et al. 1994; Manzanares et al. 1993; Spanagel et al. 1990; Widdowson and Holman 1992). Serotonin receptor antagonists and nicotinic acetylcholine receptor antagonists also block dopamine release (Blomqvist et al. 1993; Wozniak et al. 1990; Yoshimoto et al. 1992). These receptor systems and their roles in the addictive properties of alcohol are discussed later in this chapter.

GABA Receptors

GABA exerts its inhibitory effects through binding to specific receptors that form ligand-gated ion channels.[3] One type of GABA receptor, the GABA$_{\text{A}}$ receptor, comprises five molecular subunits designated alpha, beta, gamma, delta, and epsilon (Macdonald and Olsen 1994). For each subunit, a large number of molecular variants have been identified. In addition, GABA$_{\text{A}}$ receptors may be made from various combinations of subunits, indicating the potential for a large number of receptor subtypes with different pharmacologic properties.

Assembly of these subunits in the membrane endows neurons with GABA-gated chloride channels (figure 4). Upon binding to its receptor, GABA triggers the influx of negatively charged chloride ions, increasing the charge difference across the cell membrane (***hyperpolarization***) and rendering the cell less likely to fire a nerve impulse. Most sedatives, including alcohol, barbiturates, and general anesthetics, enhance the actions of GABA.

Significant research effort is currently directed toward identifying locations of alcohol-sensitive GABA receptors in the brain and clarifying the molecular mechanisms by which alcohol influences GABA receptor activities. Acute exposure to intoxicating concentrations of alcohol enhances GABA-mediated chloride flux and physiologic activity in some brain regions (Weight 1992). In general, GABA$_{\text{A}}$ receptors in the spinal cord, cerebellum, cerebral cortex, and medial septal area are more sensitive to alcohol than those in the hippocampus and lateral septal area (Criswell et al. 1993; Givens and Breese 1990). Differences in receptor subunit composition (Criswell et al. 1993; Miralles et al. 1994), activity of various protein kinase *isoforms* (Harris et al. 1995), and experimental methodology may account for some of this variation in sensitivity.

Alcohol's stimulation of GABA$_{\text{A}}$ receptor activity is thought to contribute to its anxiolytic, sedative, and motor impairment effects (Givens and Breese 1990). RO 15-4513, a drug that partially inhibits GABA chloride flux, also blocks alcohol's enhancement of GABA-mediated chloride flux and can partially reverse the ataxic and sedative effects of alcohol in some experimental animals (Suzdak et al. 1986).

Some of alcohol's effects through GABA receptors may involve phosphorylation of the receptor by PKC. In hippocampal neurons, enhancement of GABA receptor activity by alcohol has been shown to require adenosine triphosphate (ATP), a high-energy storage molecule that serves as a phosphate donor in phosphorylation reactions. This enhancement is blocked by substances that inhibit PKC activity, indicating that phosphorylation of the hippocampal GABA receptor is necessary for alcohol sensitivity (Weiner et al. 1994). Phosphorylation sites for PKC are present on two GABA receptor subunits designated beta-1 and gamma-2L (Lin et al. 1994*a*). To test the contribution of these subunits to alcohol sensitivity, researchers have examined the effects of alcohol on *Xenopus* oocytes expressing alpha-1 and beta-1 subunits in combination with gamma-2L subunits or gamma-2S subunits (which lacks a phosphorylation site). Alcohol

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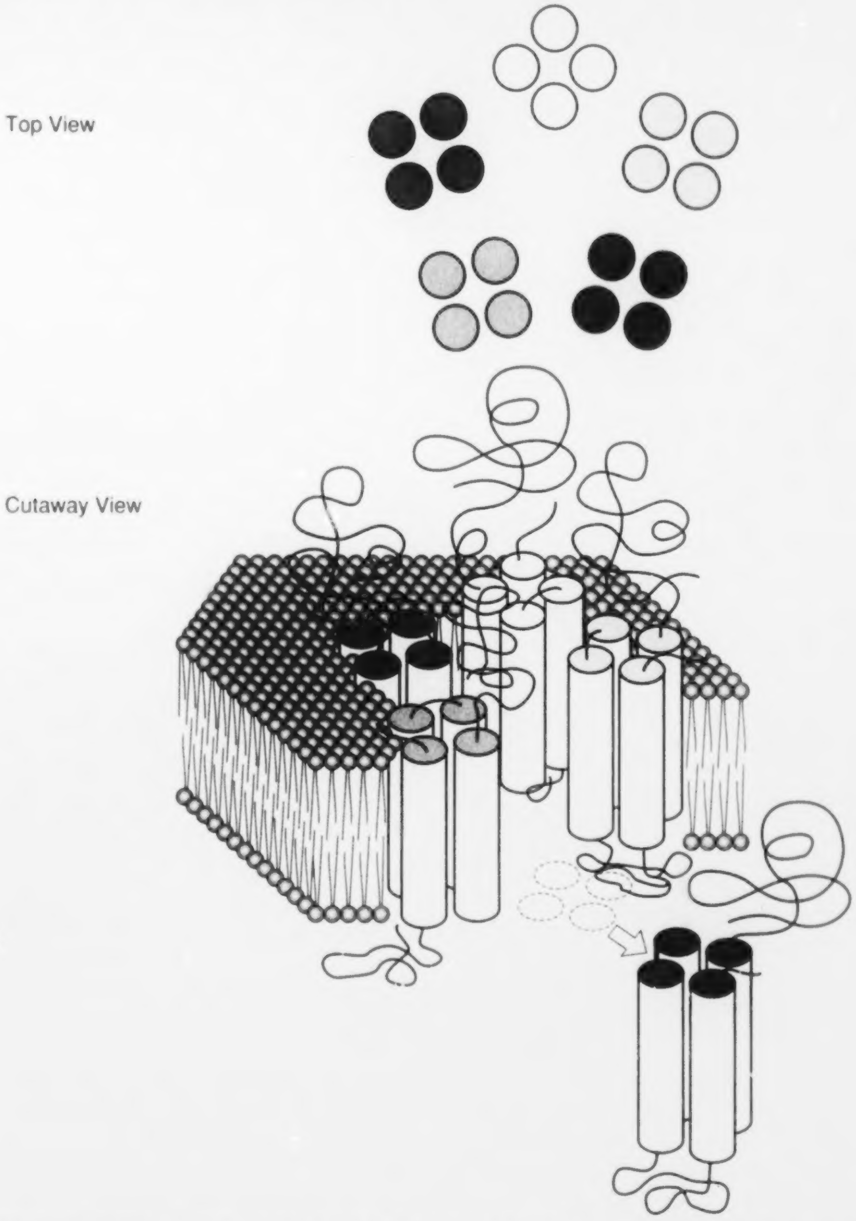
[3] Ligand-gated channels are proteins composed of five subunits clustered around a central ion channel (Unwin 1995). They contain a specific ligand-binding site, an ion selective pore that responds to ligand binding, and sites that regulate ligand binding and channel properties. Ion channels gated by neurotransmitter binding are main targets of intoxicating concentrations of alcohol.

Figure 4. Model of the $GABA_A$ receptor.

The receptor is made up of five subunits, each including four membrane-spanning regions. The membrane-spanning regions are shown as circles in the top view and as cylinders in the cutaway view. The five subunits cluster together to form an ion channel.



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enhanced GABA responses in cells expressing alpha-1, beta-1, and gamma-2L subunits but not in cells expressing alpha-1, beta-1, and gamma-2S subunits (Wafford et al. 1991). In related experiments, removal of the PKC phosphorylation site from gamma-2L (using an experimental approach known as site-directed mutagenesis) abolished the alcohol sensitivity of GABA receptors consisting of alpha-1, beta-1, and gamma-2L subunits (Wafford and Whiting 1992). These studies suggest an important role for PKC in alcohol's actions on GABA receptors (Criswell et al. 1993; Marszalec et al. 1994; Sigel et al. 1993).

Other data, however, suggest the need for further investigation. First, the requirement of gamma-2L subunits for alcohol's effects on GABA receptor responses has not been confirmed in studies using mammalian cells (Marszalec et al. 1994; Sigel et al. 1993). Second, gamma-2L subunits are found in brain regions that express both alcohol-sensitive and alcohol-insensitive GABA receptors (Criswell et al. 1993). Finally, the role of PKC in regulating GABA receptor function is unclear. For example, one study has shown that activation (defined as stimulation of enzyme activity) of some PKC isoforms can inhibit GABA-gated chloride flux in cultured oocytes expressing alpha-1, beta-1, and gamma-2L subunits (Leidenheimer et al. 1992); however, other studies have shown that an activated form of PKC can enhance GABA receptor function in cultured fibroblasts expressing these three subunits (Lin et al. 1994*a*).

The role of PKC in alcohol-enhanced GABA responses has been further explored by using an experimental approach known as the gene knockout technique. This powerful technique involves inactivating genes in mouse *germ cells*, which effectively deletes the corresponding protein, and allows the effects of the deletion to be studied in intact animals through many generations. Harris et al. (1995) have used knockout mice to show that deleting one type of PKC (gamma-PKC) abolishes alcohol-mediated enhancement of GABA-gated chloride flux in brain preparations. However, GABA receptors in mice with the gamma-PKC mutation displayed normal sensitivity to barbiturates and benzodiazepines that mimic GABA's effects (GABA *agonists*), suggesting that GABA receptor phosphorylation by gamma-PKC is a precondition for selective actions of alcohol.

The behavioral significance of the gamma-PKC mutation has also been demonstrated: Deletion of gamma-PKC shortened the duration of an alcohol-induced, but not a barbiturate-induced, loss of the righting reflex (the time required for an animal placed on its back to become upright, used as a measure of an animal's responsiveness to alcohol's sedative effects) (Harris et al. 1995). These findings underscore the central role of phosphorylation in both biochemical and behavioral effects of alcohol. Future studies using gene knockout techniques and other genetic alterations will provide insight into the molecular mechanisms behind alcohol intoxication and other CNS responses to alcohol. A greater understanding of these molecular mechanisms will enhance the rational design of drugs for the treatment of intoxication and addiction.

Another protein kinase, known as protein kinase A (PKA), may also play a role in mediating alcohol's effects on GABA receptors. Direct application of alcohol weakly reduces the firing rate of some cerebellar Purkinje neurons through actions on the $GABA_A$ receptor (Lin et al. 1994*b*). Alcohol's actions are greatly enhanced if Purkinje neurons are also treated with the neurotransmitter norepinephrine or a similar synthetic compound, isoproterenol. Norepinephrine and isoproterenol stimulate adenylate cyclase activity (Lin et al. 1993*a*, 1994*b*). Because cAMP produced by adenylate cyclase activates PKA and subsequent phosphorylation events, these observations suggest that PKA phosphorylation sensitizes the $GABA_A$ receptor to the actions of alcohol. In addition, because norepinephrine is normally released onto Purkinje cells by neurons in the *locus coeruleus*, this $GABA_A$ receptor sensitization may occur in intact animals. Moreover, alcohol reduces the reuptake of norepinephrine by nerve cells in the cerebellum (Lin et al. 1993*b*), thereby prolonging the actions of norepinephrine.

In contrast to its acute effects, chronic alcohol treatment inhibits $GABA_A$ receptor responses, as shown in cultured mammalian neurons (Mhatre and Ticku 1992). Chronic alcohol treatment also can reduce the alcohol-induced enhancement of GABA-gated chloride flux in the cerebral cortex (Devaud and Morrow 1995; Morrow et al. 1988; Sanna et al. 1993). These adaptive responses of GABA receptors may contribute to tolerance to alcohol's effects. For example, with chronic alcohol treatment resulting in behavioral tolerance, striking reductions in alcohol enhancement of GABA receptor activity have been observed (Allan and Harris 1987; Morrow et al. 1988). Because these adaptive changes in receptor activity may reflect changes in receptor expression, researchers have examined whether chronic alcohol exposure alters the expression of GABA receptor subunits. Chronic alcohol administration has been shown to decrease levels of several different GABA$_A$ receptor alpha subunits (Mhatre et al. 1993; Mhatre and Ticku 1992; Montpied et al. 1991; Morrow et al. 1990, 1992) but to increase levels of several GABA$_A$ receptor beta subunits (Mhatre and Ticku 1994). Although these changes in alpha subunits may explain the suppression of GABA receptor function observed with chronic alcohol exposure, the role of both alpha and beta subunits in the development of tolerance requires further investigation (Mhatre and Ticku 1994).

Other investigators have shown that in isolated brain cells, chronic alcohol treatment diminishes the enhancing effect of alcohol and benzodiazapines on GABA-gated chloride flux (Allan and Harris 1987; Buck and Harris 1990). Thus, chronic alcohol exposure may induce a cross-tolerance to both alcohol and benzodiazepines through effects on GABA-gated chloride channels. This adaptive response may account for the high doses of benzodiazepines needed to produce sedation in some alcoholic patients with delirium tremens (Charness et al. 1989). Further study of the GABA receptor subunits and molecular mechanisms through which alcohol influences tolerance may help in the design of pharmacologic treatments that prevent the development of tolerance or its adverse consequences.

Glutamate Receptors

Glutamate, the brain's major excitatory neurotransmitter, binds to at least three subfamilies of ligand-gated ion channels. These ion channels are distinguished by, and named for, their selective interaction with the compounds *N*-methyl-D-aspartate (NMDA), kainate (KA), and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) (Hollmann and Heinemann 1994; Schoepfer et al. 1994). Multiple genes have been *cloned* for the subunits of each subfamily, including at least seven genes for AMPA/KA receptor subunits (designated GLUR1-7), five for the NMDA receptor subunits (NMDAR1, NMDAR2A, NMDAR2B, NMDAR2C, and NMDAR2D), and two for receptor subunits that selectively interact with KA (KA1 and KA2). Alternative splicing of mRNA encoding these receptors creates further diversity within each receptor subfamily.

The glutamate receptor subtypes are differentially expressed by neurons in distinct regions of the brain (Nakanishi 1992), which may explain why glutamate receptors in different brain regions vary in sensitivity to alcohol. Receptor subtypes also differ in their physiologic and pharmacologic properties. Upon interaction with glutamate, AMPA/KA receptors *transduce* rapid synaptic responses by increasing sodium influx (Hollmann and Heinemann 1994; Schoepfer et al. 1994). In contrast, the NMDA receptor mediates synaptic responses of longer duration and is permeable to calcium, sodium, and potassium (figure 5). Magnesium blocks the NMDA receptor channel in resting neurons; with membrane depolarization, magnesium is displaced, allowing glutamate to trigger neuronal activity.

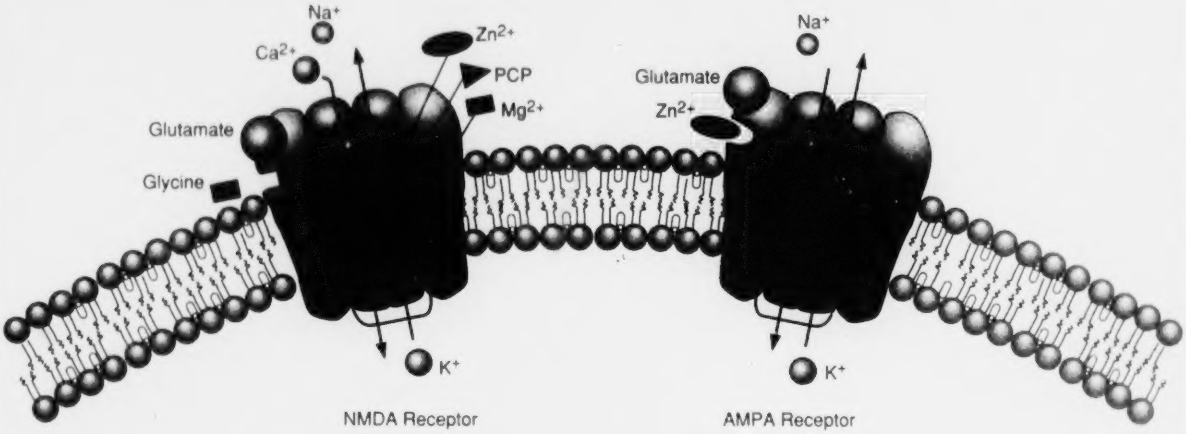
Stimulatory events mediated through glutamate receptors play an important role in various plastic CNS responses, including nervous system development, learning, and drug addiction. Excessive stimulation of NMDA receptors causes *excitotoxicity*, a process involving significant increases in intracellular calcium and cell death. Stimulation of NMDA receptors also has been associated with synthesis of nitric oxide (NO) by cortical neurons (Chandler et al. 1994). A gas with neurotransmitter and neurotoxic actions, NO has been proposed as the chemical mediator that links excitatory neurotransmission with cell death (Dawson et al. 1991). Excitotoxicity contributes to brain injury after stroke and seizures and may be involved in the neuronal cell death associated with conditions such as Alzheimer's disease, AIDS (acquired immunodeficiency syndrome) dementia complex, amyotrophic lateral sclerosis (Lou Gehrig disease), Parkinson's disease, and thiamine deficiency (Lipton and Rosenberg 1994). The NMDA receptor is equipped with multiple regulatory sites and, as a result, is subject to multiple checks and balances that prevent excitotoxicity from developing during normal synaptic function. NMDA-gated ion currents are enhanced by a second neurotransmitter, glycine, and are inhibited by magnesium and zinc. NMDA-mediated excitotoxicity also is prevented by inhibitors of NO, by the NMDA receptor antagonist dizocilpine, and by phencyclidine (angel dust) (Lipton and Rosenberg 1994).

Acute Effects of Alcohol on Glutamate Signaling

Like GABA$_A$ receptors, glutamate receptors are thought to mediate some of alcohol's intoxicating effects. The NMDA receptor is sensitive to a range of alcohol concentrations (25–250 mg/dL). Lovinger et al. (1989) showed that in cultured hippocampal neurons, alcohol reversibly inhibits ion currents gated by NMDA receptors but has little effect on ion currents gated by AMPA and KA receptors. Compared with NMDA receptors, AMPA/KA receptors are less sensitive to intoxicating

Figure 5. NMDA and AMPA receptors.

These receptors are two members of a family of receptors that bind glutamate, an excitatory neurotransmitter. Each receptor is composed of five subunits that form a channel permeable to sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+). In addition to glutamate binding sites, both receptors have binding sites for zinc (Zn^{2+}). The NMDA receptor also has binding sites for magnesium (Mg^{2+}), the neurotransmitter glycine, and the drug phencyclidine (PCP).



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concentrations of alcohol; however, when expressed as ***recombinant*** molecules in cultured mammalian cells, some AMPA/KA receptors show increased sensitivity to alcohol (Dildy-Mayfield and Harris 1992; Lovinger 1993). Other research has shown that intoxicating concentrations of alcohol selectively inhibit NMDA receptor-linked intracellular events, including the activation of guanylate cyclase, an enzyme that catalyzes production of the intracellular second messenger cGMP (Hoffman et al. 1989); release of neurotransmitters such as dopamine (Gonzales and Woodward 1990; Woodward and Gonzales 1990); and synthesis of NO (Chandler et al. 1994). In addition to its effects on the glutamate receptor, alcohol inhibits the presynaptic release of glutamate (Martin and Swartzwelder 1992) through effects on glutamate neurotransmission (Carboni et al. 1993) and indirectly through actions on other neurotransmitter systems (Clark and Dar 1989*b*; Nie et al. 1993). Inhibition of glutamate release would further reduce NMDA signaling by decreasing glutamate concentrations at the NMDA receptor.

Alcohol inhibition of NMDA signaling appears to have both physiologic and behavioral consequences. In animals, alcohol inhibits NMDA-evoked electrophysiologic activity in the medial septal area, hippocampus, inferior colliculus, and locus coeruleus but not in the lateral septal area (Engberg and Hajós 1992; Simson et al. 1993). These results suggest a differential sensitivity of NMDA receptors to alcohol in various brain regions. In addition, the locus coeruleus functions to control vigilance reactions and arousal to sensory stimuli; thus, alcohol inhibition of NMDA function in this region may explain the drug's effects on attention and sensory discrimination (Engberg and Hajós 1992). In behavioral studies, Grant and Colombo (1993) have observed that animals exhibit difficulty in differentiating between the effects of alcohol and the NMDA receptor antagonist dizocilpine in a drug discrimination test (see the discussion of drug discrimination procedures in Chapter 4, Neurobehavioral Effects of Alcohol Consumption). Taken together, the available evidence strongly suggests that alcohol-mediated inhibition of NMDA receptors plays an important role in the behavioral manifestations of intoxication.

In humans, NMDA receptors have been implicated in alcoholic blackout. People with blackouts often behave relatively normally while intoxicated, but once sober, they retain no memory of events spanning many hours. Alcohol may contribute to blackouts by disrupting CNS activities associated with long-term potentiation (LTP). LTP is a physiologic process in hippocampal neurons that serves to perpetuate neuronal activity long after the initial signal triggering this activity has dissipated. Because LTP can persist for many weeks, it is thought to be related to information storage and memory formation (Muller et al. 1988). The NMDA receptor appears to play a fundamental role in LTP, and alcohol strongly inhibits LTP, in part through its inhibition of NMDA-gated ion currents (Blitzer et al. 1990; Morrisett and Swartzwelder 1993). By this mechanism, alcohol may cause or contribute to blackouts and other memory disorders associated with alcohol misuse.

Alcohol-mediated inhibition of NMDA receptors plays an important role in the behavioral manifestations of intoxication.

Because NMDA receptor antagonists prevent excitotoxicity, and in light of alcohol's known inhibitory effects on NMDA receptor function, researchers have sought to characterize the neuroprotective actions of alcohol. Alcohol protects against NMDA neurotoxicity in cultured cortical neurons (Chandler et al. 1993*a*; Lustig et al. 1992*a,b*; Takadera et al. 1990), an effect that has been attributed to inhibition of NMDA-mediated calcium influx rather than inhibition of NO-mediated neurotoxicity (Lustig et al. 1992*b*). Alcohol also has been shown to inhibit glutamate-stimulated synthesis of NO by cultured neurons (Chandler et al. 1994). In theory, neuroprotective actions of alcohol could benefit intoxicated alcoholics during seizures, cerebral trauma, and other conditions associated with excitotoxicity. However, these potential benefits might be offset by an adaptive increase in the number of NMDA receptors that occurs with chronic drinking, as discussed later in this section.

The multiple regulatory sites found on NMDA receptors may represent molecular targets for alcohol's disruptive effects as well as potential targets for reversing these effects. Among these regulatory sites are glycine- and magnesium-binding sites. Two actions of alcohol—inhibition of NMDA-activated calcium uptake in rat cerebellar *granule cells* and inhibition of NMDA-stimulated dopamine release in rat striatal slices—can be reversed in vitro by high concentrations of glycine (Hoffman et al. 1989; Rabe and Tabakoff 1990; Woodward and Gonzales 1990). These findings suggest that alcohol competes at the glycine regulatory site to inhibit NMDA receptor function. However, studies using cultured rat hippocampal cells or hippocampal slice preparations have found that glycine and glycine agonists do not reverse alcohol inhibition of NMDA-stimulated currents or NMDA-stimulated neurotransmitter release (Peoples and Weight 1992; Woodward 1994). Similarly, alcohol, but not glycine, has been shown to reduce NMDA-mediated neurotoxicity in cultured neurons (Chandler et al. 1993*a*). Thus, the ability of glycine to reverse alcohol's effects on NMDA receptors may not be a general CNS phenomenon. In studies of magnesium-binding sites, genetic engineering of NMDAR1 receptor subunits to prevent magnesium blockage of ion channel activity had no effect on alcohol's ability to inhibit this activity (Kuner et al. 1993). These data indicate that inhibition of NMDA receptor function by alcohol does not involve its interaction with magnesium-binding sites.

Recent studies suggest that PKC participates in alcohol's effects on NMDA receptor function. In many cell types, PKC augments NMDA responses (Hollmann and Heinemann 1994). However, studies using cerebellar granule cells have shown that alcohol inhibition of NMDA-mediated increases in intracellular calcium may involve activation of PKC (Snell et al. 1994*a,b*). In addition, low concentrations of alcohol have been shown to modify the activity of two other protein kinases that regulate glutamate receptor activity (Resnicoff et al. 1993; Thurston and Shukla 1992). Continued study of alcohol's effects on the functions of protein kinases and other regulatory proteins in relation to glutamate receptor function is warranted. The recent development of mice with genetic deletions of PKC (Harris et al. 1995) will permit a direct evaluation of the role of specific forms, or isozymes, of PKC in alcohol's inhibition of glutamate receptor function.

The cloning of glutamate receptor genes has allowed researchers to examine the role of various receptor subunits in alcohol's suppressive effects. For example, various combinations of NMDA receptor subunits expressed in *Xenopus* oocytes differed in their sensitivity to alcohol (Kuner et al. 1993; Masood et al. 1994). In addition, splice variants that arise in the processing of mRNA encoding NMDAR1 subunits (Koltchine et al. 1993) show differential sensitivity to alcohol. Different NMDA receptor genes show unique patterns of subunit expression in different brain regions; hence, regional variation in the alcohol sensitivity of NMDA responses may reside in the subunit composition of the receptor (Masood et al. 1994). Differences in the expression of alcohol-sensitive and alcohol-insensitive glutamate receptors also could account for variations in sensitivity of brain NMDA receptors observed in long-sleep (LS) and short-sleep (SS) mice. LS and SS mice are strains with characteristic differences in alcohol-induced anesthesia: LS mice have an increased duration of anesthesia in response to alcohol compared with SS mice. NMDA receptors from LS mice are more sensitive to alcohol than those from SS mice (Daniell and Phillips 1994).

Pharmacologic studies have examined whether alcohol's suppressive effects on NMDA receptors result from direct interactions with receptor proteins or from indirect effects on membrane lipids. These studies suggest that alcohol interacts with a discrete *hydrophobic* pocket within the receptor protein (Peoples and Weight 1995). Alcohols of increasing chain length exhibit progressively greater lipid solubility and induce progressively larger increases in membrane fluidity. If alcohol inhibits NMDA receptor functions by disrupting membrane lipids rather than by a direct effect, then treatment with a series of alcohols varying in length from 1 carbon atom (methanol) to 10 carbon atoms (decanol) would be expected to exhibit progressively greater potency in inhibiting NMDA-gated ion currents. Instead, a "cutoff phenomenon" has been observed: Inhibition of NMDA-gated ion currents in mouse hippocampal neurons increased progressively for alcohols having 1 to 6 carbons but diminished, then disappeared with alcohols having 7 to 10 carbons. Interestingly, a similar cutoff phenomenon is observed for the intoxicating potency of various alcohols (Lyon et al. 1981; McCreery and Hunt 1978). Systematic deletion or replacement of portions of the NMDA receptor by genetic engineering may facilitate precise identification of the sites at which alcohol acts and the development of drugs that antagonize alcohol-mediated actions on the NMDA receptor.

Studies suggest that alcohol interacts with a discrete hydrophobic pocket within the NMDA receptor protein.

Chronic Effects of Alcohol on Glutamate Signaling

With long-term alcohol consumption, neuronal cells appear to compensate for alcohol's acute inhibition of NMDA receptor function. Animals treated chronically with alcohol show increased numbers of binding sites for glutamate antagonists (indicating increased expression of glutamate receptors) in brain regions associated with the generation of seizures, including the cerebral cortex, hippocampus, *striatum*, and *thalamus* (Grant et al. 1990; Gulya et al. 1991). Furthermore, post mortem comparison of human brains from alcoholics and nonalcoholics has revealed increased numbers of glutamate-binding sites in brains from alcoholics (Crews et al. 1993; Michaelis et al. 1990), suggesting that alcohol *upregulated* glutamate receptors. However, the techniques used in these studies could not identify which glutamate receptor subtypes were upregulated. More recent studies using antibody probes to identify receptor subtypes have shown that chronic alcohol ingestion increases expression of the NMDAR1 subunit (by 65 percent) in the hippocampus, but not in several other brain regions, and had no effect on levels of GLUR1 or GLUR2 subunits (Trevisan et al. 1994). Follesa and Ticku (1995) have shown that chronic alcohol treatment in rats increases levels of mRNA for two other NMDA receptor subunits, NMDAR2A and NMDAR2B, but not NMDAR1 subunits, in the cerebral cortex and hippocampus. In contrast, no such changes were observed in the cerebellum. These findings represent the first evidence that chronic alcohol treatment differentially regulates NMDA receptor subunit mRNA expression in different parts of the rat brain.

This compensatory increase in the number of glutamate receptors after long-term alcohol intake may contribute to the occurrence of alcohol withdrawal seizures (Hoffman and Tabakoff 1994). The NMDA receptor antagonist dizocilpine has been shown to prevent seizures in alcohol-dependent mice when microinjected into the inferior colliculus and pontine reticular formation, two brain regions implicated in the development of seizures (Riaz and Faingold 1994). One study has shown that treatment of alcohol-dependent mice with dizocilpine decreased the severity of alcohol withdrawal seizures but did not reduce withdrawal-associated forelimb tremors (Grant et al. 1990). Hence, alterations in NMDA signaling appears to affect only some symptoms of withdrawal.

As mentioned earlier, adaptive increases in NMDA receptors occur with chronic alcohol exposure. These increases may increase the risk of excitotoxicity (Chandler et al. 1993*b*; Crews et al. 1993). Acute alcohol treatment inhibits NMDA-mediated increases in intracellular calcium concentrations in cultured cerebellar granule cells; however, chronic alcohol treatment produces an increase in NMDA responsiveness (Iorio et al. 1992) that is consistent with increases in numbers of NMDA receptors (Hoffman et al. 1995). The adaptive response to chronic alcohol treatment counteracts alcohol's acute inhibition of NMDA receptor activity but renders cells more vulnerable to NMDA excitotoxicity (Iorio et al. 1993); in turn, this excitotoxicity could be attenuated by NMDA receptor antagonists (Hoffman et al. 1995). Related experiments using cultured cerebrocortical cells have shown that chronic treatment with alcohol also increases NMDA-induced elevations in intracellular calcium and NMDA neurotoxicity (Ahern et al. 1994). Collectively, these findings suggest that increased expression of the NMDA receptor may place alcoholics at increased risk for a spectrum of neurological disorders associated with excitotoxicity. Thus, the development of clinically effective NMDA antagonists may be useful for reducing the acute symptoms of alcohol withdrawal as well as the excitotoxic brain damage associated with seizures, head trauma, and thiamine deficiency in alcoholics.

Adaptive increases in NMDA receptors occur with chronic alcohol exposure. These increases may increase the risk of excitotoxicity.

In alcoholics, thiamine deficiency can cause Wernicke's encephalopathy, a common neurologic disorder characterized by mental confusion, ataxia, and oculomotor abnormalities. NMDA receptors have recently been implicated in the development of this disorder (Langlais and Mair 1990). In an animal model used to study thiamine deficiency, vulnerable brain structures, such as the thalamus, show markedly increased levels of glutamate prior to the development of brain lesions (Langlais and Zhang 1993). Dizocilpine was found to reduce the neurologic signs as well as the severity and extent of the lesions (Langlais and Mair 1990). These data suggest that glutamate excitotoxicity may contribute to the pathogenesis of Wernicke's encephalopathy and that NMDA receptor antagonists may improve the generally poor outcome of this disorder in humans (Charness et al. 1989).

Serotonin Receptors

Serotonin acts through several receptors, including the 5-HT$_3$ and 5-HT$_{1C}$ receptors. The 5-HT$_3$ receptor is a ligand-gated ion channel that mediates rapid synaptic transmission by increasing membrane permeability to sodium and potassium (Derkach et al. 1989). In contrast, the 5-HT$_{1C}$ receptor is linked by G proteins to a chloride channel that opens or closes in response to changes in calcium concentrations.

Alcohol appears to directly affect 5-HT$_3$ receptor function, enhancing sodium and potassium currents in neuronal cells and rat cerebral membranes (Hellevuo et al. 1991; Lovinger 1991; Lovinger and White 1991). Alcohol also amplifies currents gated by recombinant 5-HT$_3$ receptors in nonneuronal cells (Lovinger and Zhou 1994; Machu and Harris 1994), indicating that alcohol sensitivity is an intrinsic property of the channel that persists outside of a neural environment. Like the NMDA receptor, the 5-HT$_3$ receptor exhibits a cutoff in sensitivity to alcohols of increasing carbon chain lengths, suggesting a direct effect of alcohol on receptor function. The cutoff for the 5-HT$_3$ receptor occurred with alcohols having more than five carbon atoms (Peoples et al. 1996).

Similar to its effects on dopamine, alcohol stimulates the release of serotonin in the nucleus accumbens (Yoshimoto et al. 1992), an action that may contribute to the rewarding or reinforcing properties of the drug. 5-HT$_3$ antagonists block alcohol-induced dopamine release in the nucleus accumbens (Carboni et al. 1989; Wozniak et al. 1990; Yoshimoto et al. 1992) and decrease craving for alcoholic beverages in humans (Johnson et al. 1993). These findings suggest that activity of the 5-HT$_3$ receptor influences the intoxicating and addictive effects of alcohol. The localization of 5-HT$_3$ receptors in the gut and in brain regions that mediate nausea and vomiting, coupled with data showing that alcohol and some anesthetic compounds share 5-HT$_3$-enhancing effects as well as nauseating and emetic effects, suggests that alcohol may induce nausea and vomiting by stimulating 5-HT$_3$ receptor function (Machu and Harris 1994). In addition, 5-HT$_3$ receptors have been implicated in the pathogenesis of the alcohol withdrawal syndrome, based on studies demonstrating that a selective 5-HT$_3$ antagonist increased the severity of alcohol-withdrawal seizures in mice (Grant et al. 1994).

In contrast to its effects on 5HT$_3$ receptors, alcohol inhibits actions of the 5-HT$_{1C}$ receptor. Recent studies using *Xenopus* oocytes that were genetically manipulated to respond to serotonin have shown an inhibitory effect of alcohol on serotonin-sensitive chloride currents (Sanna et al. 1994). This inhibition could be reproduced by PKC activators and blocked by PKC inhibitors, indicating that alcohol exerts its suppressive effect on 5-HT$_{1C}$ receptors through activation of PKC (Sanna et al. 1994).

Other Receptors

Nicotinic Acetylcholine Receptor

The nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion channel that is activated by the neurotransmitter acetylcholine. The addictive drug nicotine is the prototypic agonist for this receptor, and because nicotine and alcohol are often abused together, researchers have attempted to identify CNS activities that are common to both drugs. For example, alcohol and nicotine release dopamine in the nucleus accumbens, and the actions of both drugs are blocked by serotonin 5-HT$_3$ antagonists (Carboni et al. 1989).

Different subtypes of nAChRs are present at the junction between nerve and muscle cells (the neuromuscular junction), at synapses of the autonomic nervous system, and in the CNS. Alcohol *potentiates* nAChR currents at the neuromuscular junction, apparently by stabilizing an open channel state (Wu et al. 1994). Furthermore, experiments in mice demonstrate that mecamyline, an nAChR antagonist, can block alcohol-induced dopamine release in the nucleus accumbens and alcohol-induced increases in locomotor activity (Blomqvist et al. 1992, 1993). The role of nAChRs in mediating the actions of alcohol and the possibility that different nAChR subunit combinations yield different responses to alcohol are areas of continuing study.

Alcohol potentiates nAChR currents at the neuromuscular junction, apparently by stabilizing an open channel state.

ATP-Gated Ion Channels

In addition to its role as an energy storage molecule, ATP can function as an excitatory neurotransmitter. ATP is packaged with neurotransmitters into synaptic vesicles, is released into the synapse after membrane depolarization, and binds specific ATP receptor-gated ion channels on postsynaptic nerve terminals (Li et al. 1993). Alcohol inhibits currents gated through this channel by weakening the binding affinity of ATP for its receptor (Li et al. 1993). Data suggest that alcohol interacts with a small hydrophobic pocket on the ATP receptor that is smaller than the alcohol-binding site on the NMDA receptor and that in contrast to its effects on NMDA receptors, alcohol inhibits ligand binding rather than ion gating (Li et al. 1994; Peoples and Weight 1995). Thus, alcohol's inhibitory actions on various excitatory ligand-gated ion channels are likely mediated through distinct binding sites and different mechanisms (Peoples and Weight 1995; Weight 1992).

Voltage-Activated Calcium Channels

Calcium's role as an intracellular messenger is critical to many cellular activities, including activation of protein kinases and other cellular enzymes, release of neurotransmitters, and modulation of ion channel permeability. Cytoplasmic levels of calcium are tightly regulated by a variety of cellular activities and membrane proteins, including the actions of voltage-activated calcium channels (VACCs).

VACCs regulate neuronal excitability and link membrane depolarization to neurotransmitter release by mediating an influx of calcium ions in response to an action potential. One type of VACC, the L-type VACC, is widely distributed in the nervous system, particularly in the cerebellum (Starr et al. 1991).

In various neural cell preparations, alcohol treatment inhibits VACC activity (Weight 1992), and studies of L-type channels suggest that this inhibition involves a shortened duration of channel opening with no effect on the rate of ion flow through the channel (Wang et al. 1994*b*). Alcohol inhibition of VACCs may contribute to reductions in neurotransmitter release in diverse brain regions and thus to acute behavioral effects of alcohol (Czarnecka and Kubik-Bogucka 1993). In most studies, VACC inhibition requires alcohol concentrations that are higher than those required for inhibition of ligand-gated ion channels (Weight 1992). Recently, however, intoxicating (i.e., physiologically relevant) concentrations of alcohol were found to inhibit L-type VACCs in nerve terminals isolated from the posterior pituitary gland, thereby reducing the release of the vasopressin (Wang et al. 1991), a *neuropeptide* with numerous functions including control of urine production.

With chronic alcohol consumption, a compensatory increase in VACC function is observed in brain tissue and cultured neural cells (Charness 1992). Much of this change is attributable to an increase in the number of VACCs (Huang and McArdle 1993; Messing et al. 1986). Studies using the neural cell line PC12 suggest that chronic alcohol treatment increases numbers of VACCs by increasing the activity and levels of PKC (Messing et al. 1991*b*; Messing et al. 1990) (discussed later). Alcohol-induced upregulation of VACCs is associated with increased neurotransmitter release, increased neuronal excitability, and development of alcohol withdrawal seizures (Whittington et al. 1992; Whittington and Little 1993). Such seizures in animals and humans can be reduced by treatment with calcium channel antagonists (Koppi et al. 1987; Little et al. 1986).

Potassium Channels

Potassium channels play a major role in regulating *membrane potential* and producing membrane repolarization following transmission of nerve impulses. Voltage-gated potassium channels, one of two main classes of potassium channels, allow both the influx and the efflux (exit) of potassium (Jan and Jan 1994). Molecular biology studies have assigned various properties of the channel, such as voltage sensing, ion selectivity, and channel inactivation rate, to specific regions of the channel protein (Jan and Jan 1994).

Numerous potassium channel subtypes have been studied as recombinant molecules in *Xenopus* oocytes. In these cells, low concentrations of alcohol reduced current amplitude for only 1 channel subtype, designated Shaw2, of 14 different channel subtypes tested (Covarrubias and Rubin 1993). The selectivity and kinetics of this effect suggested that alcohol was interacting directly and specifically with the Shaw2 channel protein, rather than with surrounding lipids (Covarrubias and Rubin 1993). The remaining 13 potassium channel subtypes were generally insensitive to concentrations of alcohol less than 1,000 mg/dL, a lethal concentration in nondrinkers (Anantharam et al. 1992; Covarrubias and Rubin 1993). However, individual channel properties showed differential sensitivity to very high concentrations (>1,000 mg/dL) of alcohol, suggesting that alcohol perturbs discrete regions of the channel protein (Anantharam et al. 1992). For one channel subtype, DRK1, genetic manipulation to delete a cytoplasmic portion of the molecule increased sensitivity to alcohol (Anantharam et al. 1992). These experiments illustrate the potential of molecular biology techniques for defining mechanisms by which alcohol perturbs cell signaling. Similar experiments involving selective mutagenesis of relevant signaling proteins will likely provide a rich source of information on the molecular attributes that endow proteins with sensitivity to alcohol and will facilitate the development of drugs that can block specific alcohol-protein interactions.

G Protein-Coupled Receptors

The binding of many different neurotransmitters to membrane receptors is coupled to changes in cellular function by a family of G proteins (Clapham 1994). G proteins are composed of three subunits (alpha, beta, and gamma) and are so named because their interaction with ligand-stimulated receptors leads to the binding of guanosine triphosphate (GTP), a high-energy molecule similar to ATP. Numerous families of G-protein subunits have been cloned and characterized. These studies have shown that different free G-alpha subunits interact selectively with specific ion channels, to control channel properties, and with enzymes such as adenylate cyclase, guanylate cyclase, and phospholipase C, to regulate the generation of intracellular second messengers (Clapham 1994). For many receptors, binding of ligand results in activation and subsequent coupling of the receptor to G proteins. G proteins then bind GTP, and their subunits dissociate as part of a ligand-responsive cascade of intracellular changes.

Among numerous G protein-coupled receptors are the opioid receptors (specifically, the delta, mu, and kappa opioid receptor subtypes). Alcohol may produce intoxication, tolerance, and physical dependence in part through effects on opioid neurotransmission (Charness 1989). Alcohol stimulates the release of opioid peptides, which in turn act through the delta opioid receptor (DOR) to release dopamine in the nucleus accumbens (Acquas et al. 1993; Gianoulakis and de Waele 1994). As discussed earlier, dopamine has been implicated in the reinforcing properties of alcohol, and in vivo studies have shown that DOR antagonists can block alcohol-induced dopamine release in the nucleus accumbens (Acquas et al. 1993). Thus, DOR antagonists may be valuable for reducing the desire to drink (Koob 1992).

In vitro studies using neural cell lines have shown that chronic alcohol treatment (115–925 mg/dL) increases the expression of DOR protein and mRNA threefold to fivefold (Charness et al. 1986, 1993). DOR upregulation persisted for 12–24 hours after alcohol withdrawal (Charness et al. 1983). Charness et al. have suggested that during this time, increased dopamine release resulting from increased opioid receptor activity may contribute to the rewarding properties associated with chronic alcohol ingestion. Chronic treatment with naloxone, an opioid receptor antagonist, also increased DOR protein and gene expression in a neural cell line, although by a mechanism different from that of alcohol (Charness et al. 1986; Jenab and Inturrisi 1994). The effects of alcohol and naloxone on DOR may have clinical relevance, in that naltrexone, another opioid antagonist, has been shown to reduce craving for alcohol in humans (Volpicelli et al. 1992) and is now approved for the treatment of alcoholism. Naltrexone may reduce alcohol intake by reducing dopamine release during intoxication and may reduce craving by increasing DOR gene expression during abstinence. A search for other drugs with similar effects on dopamine release and DOR expression may result in improved treatment of alcoholism.

Chronic alcohol exposure produces heterologous desensitization in the brain and in cultured neural cells.

Another G protein-associated receptor, the alpha$_2$-adrenergic receptor (alpha$_2$AR), is thought to play a role in alcohol intoxication and physical dependence. Studies using the neural cell line NG108-15 show that alpha$_2$AR and DOR are colocalized in membranes and couple with the same G proteins (Hu et al. 1993). Long-term treatment of NG108-15 cells with alcohol (115–925 mg/dL for 2 days) has been shown to increase alpha$_2$AR binding and alpha$_2$AR mRNA approximately threefold (Hu et al. 1993). Increases in alpha$_2$AR mRNA were first detected 6 hours after alcohol exposure (463 mg/dL), became maximal after 24 hours, and persisted for up to 5 days in the continued presence of alcohol, indicating that clinically attainable alcohol concentrations can modify alpha$_2$AR gene expression soon after exposure. Researchers have linked alcohol-induced changes in alpha$_2$-adrenergic neurotransmission with intoxication, tolerance, and physical dependence (Linnoila et al. 1987). In addition, the alpha$_2$AR partial agonist clonidine can attenuate alcohol withdrawal syndrome in humans, an effect that implicates alpha$_2$AR in withdrawal (Bjorkqvist 1975; Gold et al. 1978).

Signaling Pathways

Adenylate Cyclase

Many signaling processes are mediated by the activation of adenylate cyclase, an enzyme that converts ATP into cAMP (Taussig and Gilman 1995). In turn, cAMP activates PKA, leading to phosphorylation of a range of cellular proteins and consequently to changes in many intracellular functions. Because each step of the signaling process amplifies the initial signal, small changes in adenylate cyclase activity may produce large physiologic effects. In most instances, adenylate cyclase activity is increased by stimulatory G proteins (G_s) and suppressed by inhibitory G proteins (G_i). Signaling for many different neurotransmitters converges on the activation of common stimulatory and inhibitory G proteins. Eight different adenylate cyclase genes have been cloned, and the corresponding proteins differ in their tissue distribution and regulation by G proteins, calcium, and other protein kinases (Taussig and Gilman 1995).

Acute alcohol exposure enhances neurotransmitter stimulation of adenylate cyclase by enhancing receptor-induced activity of stimulatory G proteins (Hoffman and Tabakoff 1990). The potency and magnitude of alcohol's effect vary among different tissues and brain regions, which may reflect the differential distribution of various adenylate cyclase subtypes. In general, the effects of low alcohol concentrations (50–250 mg/dL) on adenylate cyclase activity are small, although signal amplification may produce larger physiologic changes. PKA activity appears to increase the sensitivity of cerebellar GABA receptors to alcohol's effects (Lin et al. 1993*c*, 1994*a*).

In contrast to the effects of acute alcohol exposure, chronic alcohol exposure produces heterologous desensitization, a broadly suppressive effect on the stimulation of adenylate cyclase activity by multiple hormones and neurotransmitters, in the brain and in cultured neural cells (Hoffman and Tabakoff 1990; Mochly-Rosen et al. 1988). This effect appears to compensate for alcohol's acute enhancement of cAMP accumulation and may represent a form of cellular tolerance (Gordon et al. 1986). Heterologous desensitization may also involve direct or indirect effects of alcohol on the amount or activity of adenylate cyclase (Tabakoff et al. 1995).

Among the intracellular alterations associated with alcohol-induced heterologous desensitization are reduced levels of G_s (Charness et al. 1988; Hu et al. 1993; Mochly-Rosen et al. 1988; Rabin 1993; Williams et al. 1993) and, in some instances, increased levels of G_i (Charness et al. 1988). In animal studies, chronic alcohol treatment increases levels of particular G_i subtypes in the pons and cerebellum of both LS and SS mice (Wand et al. 1993). Related experiments have shown that chronic alcohol treatment reduces levels of one G_s subtype, $G_{s\alpha}$, in the anterior pituitary of LS but not SS mice, findings that are of interest in view of the increased sensitivity of LS mice to alcohol relative to SS mice (Wand and Levine 1991). However, animal studies of chronic alcohol exposure have not shown similar decreases in $G_{s\alpha}$ in other brain regions (Pellegrino et al. 1993; Wand et al. 1993).

Changes in adenylate cyclase also are observed in alcoholics. Receptor-mediated activation of adenylate cyclase in lymphocytes (white blood cells) (Diamond et al. 1987) and platelets (Tabakoff et al. 1988) is lower in alcoholics than in nonalcoholics. In addition, in vitro alcohol treatment of lymphocytes from alcoholics was shown to induce heterologous desensitization (Nagy et al. 1988), and lymphocytes from alcoholics are more sensitive to alcohol's chronic effects than are lymphocytes from nonalcoholics. Compared with lymphocytes from actively drinking alcoholics and nonalcoholics, lymphocytes from abstinent alcoholics exhibit increased levels of one type of inhibitory G protein. This finding may account for the alcohol-mediated heterologous desensitization of adenylate cyclase observed in these cells (Waltman et al. 1993).

Phospholipase C

A second major signaling pathway that also is affected by alcohol involves phospholipase C and a family of G proteins known as $G_{q/11\alpha}$. Binding of a neurotransmitter to its receptor activates $G_{q/11\alpha}$, which then stimulates phospholipase C activity (Smrcka et al. 1991), resulting in the production of the intracellular messengers diacylglycerol and inositol triphosphate. In turn, inositol triphosphate induces the release of calcium from intracellular stores, and diacylglycerol, in combination with calcium and membrane lipid, stimulates PKC activity.

In vitro experiments have examined the influence of acute and chronic alcohol on phospholipase C signaling pathways. In cultured neural cells, acute alcohol exposure even at high (sublethal) concentrations generally does not alter receptor-mediated stimulation of phospholipase C (Smith 1993). However, long-term incubation of NG108-15 cells with alcohol has been shown to reduce phospholipase C activity stimulated by a neuropeptide and by chemical activators of $G_{q/11\alpha}$ proteins. These findings suggest that chronic alcohol treatment diminishes the amount or function of this G protein (Simonsson et al. 1991); indeed, other investigators have determined that chronic alcohol treatment of NG108-15 cells reduces $G_{q/11\alpha}$ levels (Williams and Kelly 1993). The relevance of these findings to alcohol-induced alterations in brain function, however, remains to be determined.

Protein Kinase C

As discussed earlier, the effects of alcohol on several neurotransmitter receptors are mediated indirectly through effects on PKC. Ten isozymes of PKC have been identified, each with different properties and distributions in nervous tissues (Tanaka and Nishizuka 1994). Each isozyme differs in sensitivity to alcohol, which may account for variations observed in the effects of alcohol on PKC-regulated signaling pathways.

Low concentrations of alcohol do not directly activate purified PKC or PKA (Machu et al. 1991; Slater et al. 1993). However, acute alcohol exposure can increase PKC activity in nonneuronal cells, including lymphocytes (DePetrillo and Liou 1993) and fibroblasts (Kiss and Garamszegi 1993), and in some neuronal cells, including astroglial cells (Skwish and Shain 1990). With chronic alcohol exposure, changes observed in the abundance or activity of PKC may represent adaptive mechanisms induced by alcohol. For example, increases in levels of VACCs in the brain and in cultured neural cells observed with long-term alcohol treatment are prevented by chemical inhibitors of PKC (Messing et al. 1990). In related studies, chronic alcohol treatment was found to increase PKC activity by selectively increasing the amount of two PKC isozymes, epsilon and delta PKC (Messing et al. 1991*b*). Because PKC phosphorylates a wide variety of proteins, which in turn regulate the expression of many genes, alterations in PKC could potentially alter gene expression to produce some of the enduring cellular changes associated with tolerance and physical dependence.

Alcohol stimulation of PKC also may influence neurite outgrowth, which may cause nervous system injury by disturbing the development and organization of the nervous system. With chronic alcohol intake, neurite outgrowth is observed in selected brain regions (King et al. 1988; Pentney and Quackenbush 1990). Similarly, alcohol enhances neurite outgrowth in cultured neural cells treated with nerve growth factor (NGF) and basic fibroblast growth factor (FGF), ***neurotrophins*** that promote the survival and differentiation of selected nerve cell populations (Messing et al. 1991*a*; Zou et al. 1993). This effect could be abolished by pretreatment of cells with high concentrations of phorbol esters, a chemical treatment that decreases levels of some PKC isozymes (Roivainen et al. 1993). Effects of NGF and basic FGF involve the activation of intracellular protein kinases, including an enzyme known as mitogen-activated protein kinase (MAP kinase). Alcohol appears to enhance MAP kinase activity induced by NGF and basic FGF, and reduction in PKC isozymes prevented this enhancing effect (Roivainen et al. 1995).

Thus, changes in the activity or levels of PKC isozymes observed with long-term alcohol treatment appear to be responsible for at least two important cellular changes: increased levels of VACCs and enhancement of neurotrophin-induced neurite growth. In view of the large number of actions of PKC on receptor activity, channel function, and gene transcription, it seems likely that PKC mediates additional molecular events associated with long-term alcohol treatment and that these events may contribute to alcohol-mediated adaptive responses of the nervous system. Additional research to characterize the many cellular activities and mechanisms involved may lead to the development of pharmacologic agents that act within the PKC pathway to prevent or alleviate alcohol dependence and its neurologic complications.

Adenosine Transporter

An extensive literature has implicated adenosine as a mediator of some of alcohol's behavioral effects (Dar et al. 1983; Diamond and Gordon 1994). Adenosine is a neuromodulator with predominately sedative actions, and the stimulant effects of caffeine derive principally from its properties as an adenosine receptor antagonist (Chin 1989; Snyder 1985). Adenosine interacts with adenosine receptors and nucleoside transporters. There are four known adenosine receptor subtypes, and adenosine binding results in stimulation or inhibition of adenylate cyclase and increased potassium conductance (Linden 1994) (figure 6). Adenosine's synaptic actions are terminated primarily by reuptake into nerve cells by nucleoside transporters (Diamond and Gordon 1994). Alcohol blocks the reuptake of adenosine, leading to its extracellular accumulation (Clark and Dar 1989*a*; Nagy et al. 1990). Alcohol also enhances the stimulation of cAMP accumulation by one type of adenosine receptor, known as the A_2 receptor (Gordon et al. 1986). These pharmacologic actions likely explain the ability of adenosine antagonists, such as caffeine, to reduce alcohol-induced motor incoordination and sedation (Clark and Dar 1988; Dar et al. 1983). An increased understanding of the molecular basis of adenosine's actions could lead to the development of improved selective antagonists of alcohol's effects.

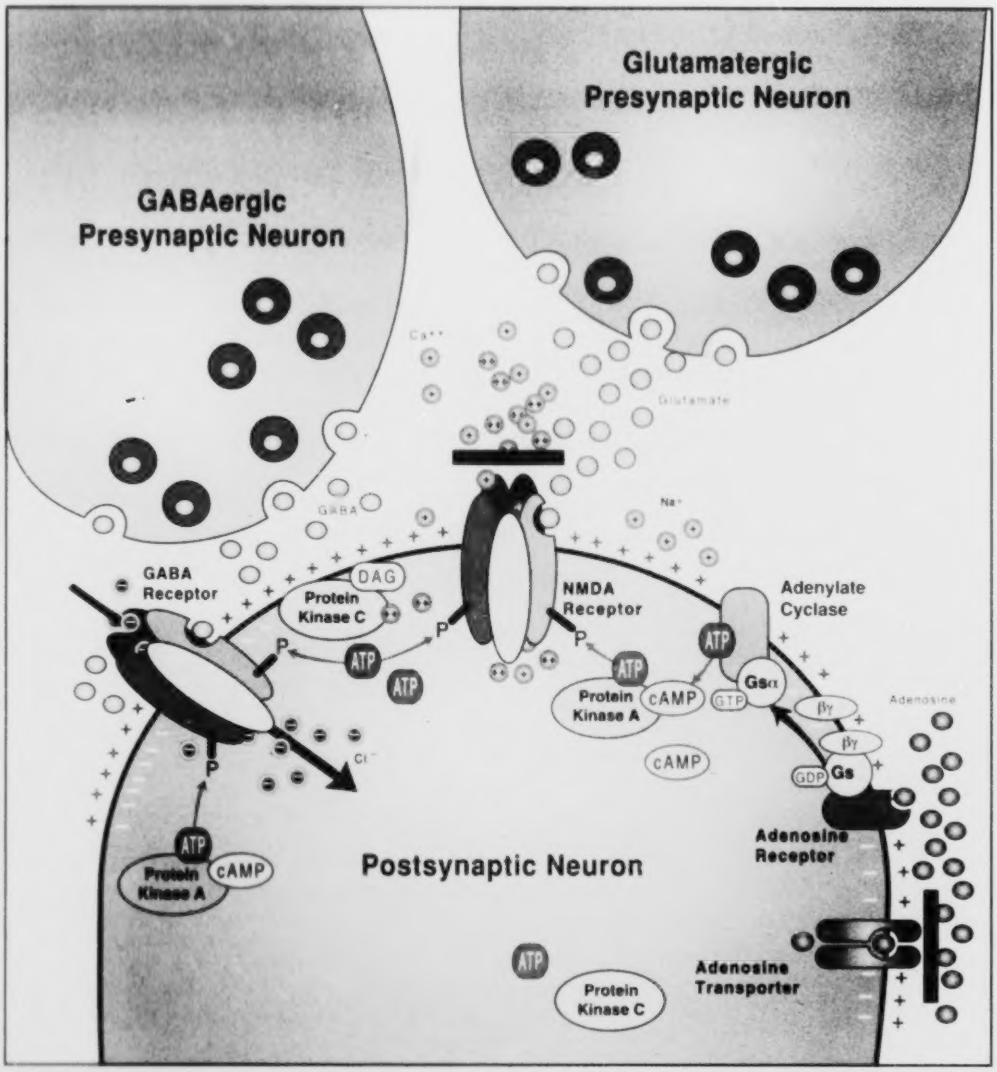
Recent work has established that alcohol inhibits just one member of the family of nucleoside transporters that carry extracellular adenosine into the cell (Krauss et al. 1993). Alcohol-mediated inhibition is dependent on PKA activity, suggesting that alcohol interacts only with the phosphorylated form of the transporter (Nagy et al. 1991).

Acetate, produced during alcohol metabolism, may be further metabolized to adenosine, which may exert neuropharmacologic effects through actions at adenosine receptors (Cullen and Carlen 1992; Israel et al. 1994; Phillis et al. 1992). Thus, alcohol administration may enhance adenosine neurotransmission in at least three ways: inhibition of adenosine uptake into cells, potentiation of adenosine A_2 receptor activity, and synthesis of adenosine from acetate (Israel et al. 1994).

In some cells, alcohol's acute inhibition of adenosine transport appears to be linked to the development of heterologous desensitization that develops with chronic alcohol exposure (Nagy et al. 1989). Heterologous desensitization of adenylate cyclase could be prevented in the neural cell line NG108-15 by incubating slowly dividing cells with adenosine deaminase (an enzyme that breaks down extracellular adenosine) and was not observed in mutant cells that lack adenosine transporters (Nagy et al. 1989). Moreover, a selective adenosine receptor antagonist, BW 1434U, prevented the stimulation of cAMP accumulation by acute alcohol treatment and the development of heterologous desensitization during chronic alcohol treatment (Sapru et al. 1994). In contrast, metabolism of adenosine did not block heter-

Figure 6. Actions of alcohol on signal transduction pathways.

Alcohol alters the function of a variety of membrane and intracellular proteins associated with the postsynaptic neuron, including receptors and enzymes involved in the production of second messengers. Alcohol enhances the movement of negatively charged chloride ions into the cell (*thick black arrow*) when GABA* binds to its receptor and inhibits the movement of positively charged sodium ions (Na^+) and calcium ions (Ca^{++}) into the cell (*thick black bar at center*) when glutamate binds to the NMDA receptor. The resulting alteration in the charge differential across the membrane causes a decrease in neuronal excitability. Phosphorylation of the GABA and NMDA receptors by protein kinase C and protein kinase A may facilitate alcohol's actions on ion flux. Alcohol also blocks the uptake of adenosine into neurons through actions on the adenosine transporter (*thick black bar at right*). As a result, adenosine accumulates in the extracellular space and binds to adenosine receptors, which activate the stimulatory G protein $G_{s\alpha}$. In addition, alcohol potentiates the activation of adenylate cyclase by $G_{s\alpha}$, leading to accumulation of the second messenger cAMP, activation of protein kinase A, and phosphorylation of diverse cellular proteins. The cellular proteins depicted here are a subset of those that mediate intoxication. The proteins that mediate alcohol's effects likely vary among different cell types, depending upon their expression of specific receptor subunits and protein kinase subtypes.


Glutamatergic Presynaptic Neuron
GABAergic Presynaptic Neuron
Ca++
Glutamate
GABA
Na+
GABA Receptor
DAG
Protein Kinase C
NMDA Receptor
Adenylate Cyclase
P
ATP
Protein Kinase A
cAMP
GTP
Gsα
βγ
Adenosine
GDP
Gs
Cl⁻
Adenosine Receptor
Postsynaptic Neuron
Adenosine Transporter
Protein Kinase C

*GABA = gamma-aminobutyric acid, NMDA = *N*-methyl-D-aspartate, cAMP = cyclic adenosine monophosphate, DAG = diacylglycerol, ATP = adenosine triphosphate, GTP = guanosine triphosphate, GDP = guanosine diphosphate.

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ologous desensitization in rapidly dividing NG108-15 cells (Williams et al. 1993) or in another neural cell line, PC12 (Rabin et al. 1993). In related experiments, alcohol-induced heterologous desensitization of adenyate cyclase and reductions in $G_{s\alpha}$ were observed in normal PC12 cells but not in PC12 cells deficient in PKA (Rabin 1993; Rabin et al. 1992). These findings suggest that PKA signaling pathways are important in cellular adaptive responses to alcohol. However, the precise mechanisms involved appear to vary among different tissues and under various experimental conditions.

Cell-Cell Interactions

Contact between cells is regulated by cell adhesion molecules—membrane proteins that protrude into the extracellular space and bind to similar molecules on adjacent cells. These cell-cell interactions are critical for normal development, maintenance, and repair processes of the nervous system, and adhesion molecules appear to be yet another target for alcohol.

Experiments using cultured neural cells have shown that treatment with a growth-promoting substance (osteogenic protein-1 [OP-1]), induces synthesis of two neural cell adhesion molecules, N-CAM and L1, thereby increasing cell adhesiveness (Perides et al. 1993). Alcohol treatment inhibited cell-cell adhesion in OP-1-treated cells in a dose-dependent manner; furthermore, inhibition was obtained at alcohol concentrations corresponding to BACs typically observed with consumption of a single drink (Charness et al. 1994). N-CAM and L1 both play important roles in nervous system development; thus, their disruption by alcohol may contribute to brain lesions observed in fetal alcohol syndrome. Because N-CAM and L1 are also necessary for the development of LTP (Lüthl et al. 1994), alcohol-induced inhibition of L1-mediated and N-CAM-mediated interactions may contribute to alcohol-associated memory disorders. The striking sensitivity of cell-cell adhesion to alcohol suggests that cell adhesion molecules may be valuable and relevant model proteins for studying how alcohol disrupts protein function.

Gene Expression

Membrane depolarization and protein phosphorylation are rapid and reversible events that are well suited for mediating momentary changes in neuronal signaling. More enduring changes in cell function and structure frequently require changes in gene transcription and protein synthesis. In the nervous system, changes in gene expression are thought to accompany plastic responses such as learning. The view that drug addiction may also be a plastic nervous system response has prompted studies that examine alcohol-induced changes in gene expression and the identification of genes regulated by alcohol (Miles et al. 1991, 1992; Nestler et al. 1993).

Gene transcription is regulated by transcription factors—proteins that bind to specific nucleotide sequences (regulatory regions) found within genes to control the rate at which DNA is copied into mRNA (Papavassiliou 1995). Some transcription factors, such as the cAMP-responsive element nuclear binding protein (Sassone-Corsi et al. 1988), are activated by phosphorylation, suggesting a link between alcohol-induced changes in second messenger production and changes in gene transcription. Alcohol has been shown to increase the rate of gene transcription for a variety of proteins. Two examples are tyrosine hydroxylase (Gayer et al. 1991), an enzyme critical to the synthesis of norepinephrine and dopamine, and Hsc70 (Miles et al. 1991), a *heat shock protein.*

Induction of transcription factors may play a role in the development of alcohol withdrawal seizures. Like seizures of other etiologies, alcohol withdrawal seizures induce expression of a class of genes known as immediate early genes in the brain (Dave et al. 1990). Among the immediate early genes are *c-fos* and *c-jun.* Changes in neuronal activity stimulates transcription of these genes, yielding transcription factors that regulate the expression of a wide spectrum of genes involved in plastic responses of the nervous system. Both injection of NMDA and induction of alcohol withdrawal have been shown to increase expression of the *c-fos* gene in similar brain regions, including the hippocampus (Morgan et al. 1992). Induction of *c-fos* expression by alcohol withdrawal could be blocked by the NMDA antagonist dizocilpine, suggesting that alcohol withdrawal acts in this process by activating NMDA receptors (Morgan et al. 1992). Alcohol withdrawal seizures typically occur in humans after years of drinking and repeated episodes of alcohol withdrawal (Ballenger and Post 1978). It has been postulated that repeated induction of immediate early genes may play a role in increasing the brain's susceptibility to seizures after multiple withdrawal episodes, and a better understanding of these molecular mechanisms may lead to safer methods of detoxification. (See Chapter 2, Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse, for a more detailed examination of the molecular correlates of alcohol use.)

Among other alcohol-responsive genes identified to date are those that encode molecular chaperons—proteins that regulate the trafficking of proteins during their synthesis and insertion into different cellular compartments (Miles et al. 1994). Increases in the abundance of these proteins may account for alcohol-induced changes observed in protein trafficking (Tuma et al. 1991). Miles et al. (1993) have found that alcohol induces expression of a gene encoding phosducin-like protein, which resembles phosducin, a regulator of G-protein function. These investigators suggest that induction of phosducin-like protein by alcohol may produce widespread changes in G protein-mediated signal transduction, with potentially profound effects on cellular function.

Continued progress in the identification and characterization of these and other alcohol-responsive genes will provide clues about the cellular and molecular mechanisms involved in alcohol's diverse effects on CNS activities and, ultimately, may aid in the design of pharmacologic agents that prevent or alleviate the devastating manifestations of alcoholism and alcohol dependence.

Summary

A fundamental goal of alcohol research is to define, at a cellular and molecular level, how alcohol produces intoxication, tolerance, dependence, withdrawal, and other short- and long-term behavioral and physiologic changes. Advances in neuroscience research have brought about remarkable progress toward this goal. Newly developed research techniques have allowed examination of alcohol's effects on the proteins and genes that control CNS functions. These approaches have characterized many of the molecular actions of alcohol in relation to the behavioral manifestations of its use and abuse and have provided clues toward developing new pharmacologic strategies for the prevention and treatment of alcoholism.

Unlike other psychotropic drugs, alcohol does not act through a single receptor. Rather, it may interact with and alter the function of many different cellular components, including cell membranes, neurotransmitter receptors, intracellular signaling enzymes, and genes. As a result, alcohol may have diverse and profound effects on nerve cell function.

The chemical and structural nature of cell membranes render them readily permeable to alcohol. Thus, alcohol has access to and may directly perturb the function of proteins outside the cell, in the cell membrane, or within the cell. Alcohol can alter the fluidity and electrical properties of membranes; with long-term alcohol exposure, significant reorganization of membrane components is observed. Changes in membrane properties may, in turn, alter the shape, interactions, and functions of membrane proteins. In addition, alcohol may interact directly with proteins to disrupt their normal functions.

Primary protein targets of alcohol's actions are the ligand-gated ion channels that serve as receptors for GABA, glutamate, serotonin, and ATP. Many of the intoxicating properties of alcohol result from its effects on receptors that interact with GABA, the brain's major inhibitory neurotransmitter, and glutamate, the brain's major excitatory neurotransmitter. The combined actions of GABA and glutamate through their respective receptors produce short-term changes in membrane electrical potential, firing of nerve impulses, and release of many neurotransmitters. Alcohol stimulates GABA receptor function and inhibits glutamate receptor function, yielding potentially profound effects on these various nervous system activities.

One type of GABA receptor, the GABA$_A$ receptor, is widely distributed in brain tissues. However, alcohol sensitivity of GABA$_A$ receptors is observed only in certain brain regions, possibly as a result of variation in the different subunit combinations that make up GABA$_A$ receptors. Phosphorylation of GABA$_A$ receptors by PKC increases their sensitivity to alcohol's effects, as shown in cultured cells and studies of knockout mice that lack functional genes encoding this enzyme. Deletion of PKC in these animals abolished alcohol-induced enhancement of GABA-gated chloride flux and reduced alcohol-induced anesthesia. GABA$_A$ receptors also play a role in tolerance to alcohol's intoxicating properties: With chronic alcohol exposure, GABA_A receptors become less responsive to alcohol stimulation, an effect that may result from changes in the expression of receptor subunits.

Like GABA receptors, glutamate receptors may be composed of different subunit combinations that vary in sensitivity to alcohol. For the NMDA subfamily of glutamate receptors, observed variations in receptor subunit combinations may explain variations in alcohol responsiveness of different brain regions. As for GABA receptors, PKC may play a role in alcohol's acute inhibitory actions on NMDA receptor functions. Possible effects of acute alcohol exposure on NMDA receptor function include interference with brain processes critical to the consolidation of new memories, suggesting a role for NMDA receptors in alcoholic blackouts and other alcohol-associated memory disorders. Chronic alcohol exposure increases numbers of NMDA receptors in brain tissues, an adaptive response that may compensate for alcohol-induced inhibition of NMDA receptor function. However, this increase in NMDA receptor expression also may contribute to the development of seizures during alcohol withdrawal and may render neurons more vulnerable to excitotoxic cell death.

Other alcohol-sensitive ligand-gated ion channels include serotonin 5-HT_3 receptors and ATP receptors. Alcohol appears to enhance activities of 5-HT_3 receptors but suppresses activities of ATP receptors. The 5-HT_3 receptor has been implicated in the intoxicating and reinforcing properties of alcohol, and 5-HT_3 receptor antagonists can decrease craving for alcoholic beverages in humans. Although pharmacologic studies indicate that alcohol acts directly on these ligand-gated ion channels to alter their functions, the role of 5-HT_3 receptors and ATP receptors in intoxication and other responses to alcohol require further investigation.

Alcohol may produce intoxication and dependence in part through direct or indirect effects on opioid receptors. Treatment of cells with alcohol in vitro increases the expression of one type of opioid receptor, the delta opioid receptor. In addition, alcohol causes the release of opioids, such as enkephalins and endorphins, in the brain. Binding of opioids to delta opioid receptors promotes dopamine release in the nucleus accumbens, an effect that may contribute to the euphoric and other pleasant feelings experienced with intoxication. These brain activities have been implicated in the reinforcing properties of alcohol. The opioid receptor antagonist naltrexone is thought to block dopamine release and has proven therapeutic efficacy in reducing craving for alcohol.

Within nerve cells, alcohol can disrupt multiple elements of signal transduction. For example, acute alcohol exposure increases receptor-stimulated adenylate cyclase activity. In contrast, chronic alcohol exposure inhibits the activation of adenylate cyclase by many different neurotransmitters, an adaptive process known as heterologous desensitization. The mechanisms involved in alcohol-induced heterologous desensitization vary among cell types but include decreases in levels of stimulatory G proteins; increases in levels of inhibitory G proteins; and, possibly, direct effects of alcohol on the amount or activity of adenylate cyclase. This heterologous desensitization appears to compensate for alcohol's acute effects on adenylate cyclase activity and may represent a form of cellular tolerance.

Activities of PKC, another crucial participant in intracellular signaling reactions, are also influenced by acute and chronic alcohol exposure. With chronic alcohol exposure, observed increases in PKC isozymes may mediate several adaptive responses to alcohol, including increased levels of VACCs and enhancement of neurite outgrowth by neurotrophins. Alcohol-induced increases in VACCs are associated with increased neurotransmitter release, increased neuronal excitability, and development of alcohol withdrawal seizures, and calcium channel antagonists have been shown to reduce alcohol withdrawal convulsions in both humans and animals. Neurite outgrowth may contribute to alcohol-associated brain injury by disturbing the development and organization of the CNS. The extensive role of PKC in regulating diverse cellular functions, including the activity of various other membrane proteins as well as DNA transcription and protein synthesis, suggests that increases in PKC activity may contribute to many other alcohol-associated adaptive responses of the CNS.

Effects of alcohol on gene transcription and protein synthesis may be responsible for some of the more enduring alcohol-associated changes in nerve cell function. Numerous alcohol responsive genes have been identified, and some have been cloned and characterized. Among these are the genes for molecular chaperones, proteins that regulate the trafficking of other proteins within cells. Long-term alcohol treatment induces expression of genes encoding molecular chaperons, which may in turn alter the processing and targeting of a host of cellular proteins. Alcohol also increases transcription of the gene encoding tyrosine hydroxylase, an enzyme critical for the synthesis of the neurotransmitters dopamine and norepinephrine. Further research to characterize these and other alcohol-responsive genes will provide clues about persistent CNS changes associated with alcohol use.

Through its actions on many different cellular components and activities, alcohol produces a diverse array of immediate and long-term alterations in CNS function. Continued research to identify and characterize molecular targets and cellular processes affected by alcohol will help reveal the mechanisms behind alcohol-induced intoxication, tolerance, dependence, and withdrawal and will aid in the development of agents that can offset or alleviate the harmful consequences of alcohol use.

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Chapter 4

Neurobehavioral Effects of Alcohol Consumption

Introduction

In recent years, neuroscience research has significantly increased our knowledge of the brain structures and functions affected by alcohol. A central goal of this research is to identify the neurobiological mechanisms and mediators that may underlie alcohol's short- and long-term behavioral changes. Alcohol consumption can produce euphoria; reduce anxiety; and, in some individuals, induce aggression. Long-term alcohol use can lead to alcohol dependence and may produce deficits in attention, learning, and memory.

An important focus of research on alcohol's effects on the brain is to study brain functions that motivate some individuals to drink; that is, to identify brain structures and neurochemical pathways that support the reinforcing actions of alcohol. The term "reinforcement" describes the process by which an effect resulting from a particular behavior increases the probability that that behavior will recur. A person learns a behavior, such as drinking alcohol, to obtain a particular outcome or reinforcer, such as the relaxing effects or the mild euphoria produced by alcohol. Alcohol's capacity to act as a reinforcer lies in its ability to induce subjectively pleasurable effects and ameliorate negative emotional states, such as tension, anxiety, or dysphoria. Insights gained from previous research clearly show that the conditions that make excessive alcohol consumption a reinforcing event in some individuals and not others are complex and likely involve interactions among genetic, environmental, and neurobiological factors.

To study possible links between alcohol-induced brain changes and alcohol-associated behaviors, researchers have developed numerous animal models and sophisticated behavioral and biochemical tests. Research using these tools has shown that alcohol interacts with many *neurotransmitter*[1] pathways, resulting in alterations in diverse brain functions and behaviors. In particular, selectively bred rodent lines with a genetic preference for alcohol, advanced behavioral analyses, and newly developed bioanalytical methods have provided important information about multiple brain neurochemical mechanisms with which alcohol interacts and that appear responsible for maintaining the desire and motivation to drink.

This chapter reviews significant research findings describing behaviors and underlying brain mechanisms associated with alcohol use, along with the animal models and techniques used to generate this information. In addition, the chapter discusses gender differences in alcohol's effects and associated behaviors and explains how alcohol produces aggression and deficits in memory and learning. A detailed review of research describing neurophysiologic and neuropharmacologic effects of alcohol is provided in Chapter 3, Actions of Alcohol on the Brain.

Approaches for Studying Alcohol-Seeking Behavior and Alcohol Reinforcement

Alcohol-seeking behavior has emerged as a primary behavioral measure of interest in contemporary research on alcohol abuse and addiction. Studies in this area investigate behaviors associated with obtaining access to and consuming alcohol. Such studies have identified neurobiological, genetic, environmental, and motivational factors that contribute to drinking behaviors and have been instrumental in evaluating pharmacologic agents for attenuating alcohol-seeking behavior.

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[1] For a definition of *neurotransmitter* and other terms in this chapter, see the glossary.

Although the factors that motivate alcohol-seeking behavior are not completely understood, alcohol's reinforcing properties likely play a prominent role. For example, the mood-elevating (sometimes referred to as "euphoric" or "euphorogenic") and tension-reducing effects produced by alcohol are rewarding and may encourage a person to seek alcohol and drink again. Thus, the ability of alcohol to act as a reinforcer may contribute significantly to chronic drinking, alcohol dependence, and relapse to drinking in patients recovering from alcoholism.

Alcohol Self-Administration

Although alcoholism is a condition unique to humans, researchers have expended considerable effort toward developing procedures that will induce alcohol consumption in animals. These animals are used as a tool to study alcohol-seeking behavior in humans. The importance of animal models of alcohol self-administration lies in their ability to demonstrate that alcohol serves as a reinforcer and their utility in determining the factors that underlie or modify the motivation to consume alcohol. Specifically, these models are instrumental for characterizing the reinforcing properties of alcohol, analyzing drinking patterns in animals, and analyzing the genetic determinants of alcohol preference. Such models have provided valuable information about how environmental factors, such as the availability of alternative reinforcers, the "cost" of alcohol, and stress, influence drinking and interact with genetic propensity toward excessive alcohol drinking. In general, animal models are useful for studying alcohol-associated behaviors because genetic background and experimental conditions can be carefully controlled to accommodate the study of a particular behavioral or neurochemical change induced by the drug. However, none of the available animal models can precisely mimic all of the features of human alcoholism.

Approaches frequently used to study alcohol self-administration in animals include those in which access to alcohol is freely provided and those involving operant procedures. In operant models of self-administration, access to alcohol is contingent on the performance of a distinct behavioral response, such as pressing a lever. For both approaches, alcohol is said to serve as a reinforcer if (1) alcohol is consumed in greater quantities than a concurrently offered nondrug fluid, usually water or a sweetened solution, and (2) alcohol intake results in a measurable, pharmacologically meaningful blood alcohol concentration, or BAC (i.e., concentrations known to have *anxiolytic* or other specific behavioral effects) (see Weiss and Koob 1991 for a review). Spontaneous alcohol consumption in animals is usually low, except in animals genetically selected for alcohol preference. However, researchers have shown that after an animal's "acclimation" to alcohol's aversive taste or smell, the drug can become a reinforcing, self-administered substance for several species, including monkeys, rats, and mice (see Samson et al. 1988 and Grant 1995 for reviews).

Studies of animals that self-administer alcohol have revealed an important distinction between simple preference for alcohol and operant behavior maintained by offering alcohol as a reward. Alcohol preference is typically established by determining which of two freely available solutions—alcohol and a nondrug reinforcer, such as sweetened water—animals will preferentially ingest. This task involves little learning and work. In contrast, operant behavior maintained by alcohol requires the completion of learned sequences of behavior under restrictive conditions to gain access to alcohol. In tests of operant behavior, the amount of alcohol consumed is influenced by the amount of work an animal is willing to perform. Thus, beyond establishing preference for alcohol, procedures involving operant behavior probe an animal's motivation or persistence in the effort to obtain alcohol at a particular time or within a particular set of conditions.

The importance of this distinction has been illustrated in a series of experiments that examined the extent to which alcohol served as a reinforcer in several lines of rats selectively bred for high or low alcohol consumption in alcohol preference tests, specifically alcohol-preferring (P), alcohol-nonpreferring (NP), high alcohol drinking (HAD), and low alcohol drinking (LAD) rats (see the *Eighth Special Report to the U.S. Congress on Alcohol and Health* for a discussion of genetically selected animal models used in alcohol studies). First, researchers observed that, with operant models of self-adminstration, alcohol served as a reinforcer in NP rats, which normally avoid alcohol in preference tests (Files et al. 1993*c*; Rassnick et al. 1993*a*; Ritz et al. 1994). In addition, when the number of responses required to obtain alcohol was progressively increased to the point where animals ceased responding, NP rats were willing to work harder than HAD rats (a line that typically shows high alcohol intake

Glossary

Afferent—A nerve that transmits impulses from the periphery toward the central nervous system.

Agonist—An agent that mimics the actions or effects of another agent (e.g., a drug that mimics the effects of a *neurotransmitter*).

Amygdala—An almond-shaped structure found within the tip of the temporal lobe of the brain. The amygdala is part of the limbic system and has connections to the *hippocampus*, septal area, thalamus, and *hypothalamus*.

Antagonist—An agent that blocks or reverses the actions or effects of another agent (e.g., a drug that blocks the effects of a *neurotransmitter*).

Anxiogenic—Anxiety inducing.

Anxiolytic—Anxiety reducing.

Arginine vasopressin—A form of vasopressin found in most mammals that contains argenine.

Autonomic—Pertaining to the autonomic nervous system, or that portion of the nervous system concerned with regulating the activity of smooth muscle, cardiac muscle, and glands.

Dopaminergic—Relating to *neurons* or nerve fibers that respond to dopamine.

Efferent—A nerve that transmits impulses from the central nervous system toward the periphery; for example, a motor nerve.

Endorphins—Small *neuropeptides* that bind to *opioid* receptors in the brain and have strong analgesic activity.

Enkephalins—Small *neuropeptides* that bind to *opioid* receptors in many locations in the brain and spinal cord and participate in the regulation of movement, mood, behavior, neuroendocrine regulation, and perception of pain.

GABAergic—Relating to *neurons* or nerve fibers that respond to gamma-aminobutyric acid (GABA).

Gonadal steroids—Male and female sex steroids, such as estrogen and testosterone.

Hippocampus—A curved ridge found within the cerebral hemisphere that functions in consolidation of new memories.

Hypothalamus—A region of the brain that is involved in basic behavioral and physiologic functions. These functions are critical to the maintenance of the internal environment in response to stress and other stimuli and are implicated in hunger, thirst, and heightened emotional drives.

Inverse agonist—An agent whose effects are exactly the opposite of those of an agent with which it is being compared. For example, alcohol has anxiety-reducing effects, whereas the partial inverse agonist of alcohol, RO 15-4513, not only blocks this effect of alcohol but also produces anxiety and stress when given alone.

Ions—Small, electrically charged molecules.

Mineralocorticosteroid—A *steroid* released by the adrenal glands that is involved in regulation of salt and water balance.

Neuron—A nerve cell.

Neuropeptide—Molecules composed of short chains of amino acids, such as *endorphins* and *enkephalins*, that are found in brain tissues and are thought to act as *neurotransmitters*.

Neuromodulator—A substance other than a *neurotransmitter* that is released by a *neuron* and conveys information to adjacent or distant neurons.

Neurotransmitter—A chemical messenger released by an excited or stimulated nerve cell. After being released, neurotransmitters travel across a synapse and then bind to a receptor on an adjacent nerve cell, usually triggering a series of chemical and electrical changes in the second cell.

Neurotrophic factor—A substance that promotes the survival, growth, and differentiation of selected neuronal populations.

Nucleus accumbens—A brain structure affected by many drugs of abuse and implicated in the rewarding properties of addictive drugs.

Opioid—Any of a group of peptides, such as *endorphins* and *enkephalins*, that bind to or otherwise influence opiate receptors in the brain.

Potentiate—To make more effective or active.

Psychomotor—Relating to the mental origin of muscular movement.

Receptor—A complex protein structure that recognizes and binds *neurotransmitters* or interacts with specific enzymes.

Septal area—A region that stretches as a thin sheet within the cerebral hemisphere and has functional connections with the *hypothalamus* and *hippocampus*.

Steroid—A large family of fat-soluble substances that includes many hormones and vitamins.

Ventral tegmental area—The midbrain region containing dopamine cell bodies that project to the *nucleus accumbens*.

in preference tests) to obtain alcohol (Ritz et al. 1994). Interestingly, findings from an earlier study had shown a reduced "willingness" to work for alcohol under higher response requirements in the "alcohol-preferring" AA (ALKO Alcohol) rats (Ritz et al. 1989). LAD rats, which show little alcohol intake in preference tests, showed the lowest level of responding for alcohol across all experimental conditions. In contrast, P rats consumed greater amounts of alcohol and maintained responding for alcohol at rates greater than those shown by NP, HAD, or LAD rats. Thus, only for P and LAD rats was alcohol intake in operant procedures clearly consistent with alcohol consumption in preference tests.

Taken together, these studies suggest that alcohol preference is not always predictive of whether or to what extent alcohol serves as a reinforcer in operant tasks. In other words, inherited and perhaps environmental factors that determine whether alcohol will serve as a reinforcer per se (i.e., in preference tests) differ from those that mediate the motivational value of alcohol (as inferred from the amount of work that an animal will expend to gain access to the drug). Such findings demonstrate the importance of studying the motivational underpinnings of alcohol drinking in the search to identify the antecedents of alcohol-seeking behavior and to develop treatments for alcoholism.

Research exploring various environmental determinants that induce or maintain alcohol-seeking behavior has identified such factors as changes in the palatability of the alcohol solution (Samson 1986), the concurrent availability of another desirable reinforcer (Files et al. 1993*b*), the concentration of alcohol (Beardsley et al. 1993; Samson et al. 1992), and the degree of access to alcohol (i.e., unlimited or restricted to a specified period of time each day) (Files et al. 1994). Presumably, these environmental factors influence the efficacy of alcohol to act as a reinforcer.

An additional environmental factor, the cost of alcohol, has been studied in animals by using a "closed economy" model. In this model, all daily nutritional and fluid supplies as well as alcohol are available only on the basis of work (i.e., through operant responding). This approach has shown that varying the cost of alcohol, as defined by the amount of work the animals are willing to perform to obtain the drug, affects alcohol intake in P rats compared with rats not selected for alcohol preference (Files et al. 1993*a*). For both the P rats and the nonselected rat strain, with variation in either the concentration of an alcohol solution or the number of lever presses required by the rats to obtain alcohol reinforcers, increases in alcohol concentration as well as decreases in the amount of work required to obtain alcohol enhanced total daily alcohol intake. Consumption was greatest, however, when the cost per reinforcer was lowest; that is, under conditions that simultaneously held work requirements low and alcohol concentration high. Thus, alcohol intake could be modified by the environmental variable, cost, in both strains of rats. Overall, P rats worked about 10 times harder for the reinforcer and consumed greater volumes of alcohol than nonselected rats, indicating an association between a genetic predisposition for high alcohol intake and a greater motivation to work for alcohol.

In a related study, Beardsley et al. (1993) examined the effect of alcohol concentration on the persistence with which animals would work to obtain alcohol. Persistence can be determined by adjusting time intervals between alcohol availability in operant procedures. The researchers found that increasing the concentration of alcohol enhances alcohol intake and makes self-administration more persistent. When the time interval between alcohol availability was lengthened, a procedure that normally reduces responding for alcohol, increases in alcohol concentration made alcohol-seeking behavior more resistant to this disruption.

Studies concerned with the influence of environmental factors that contribute to the initiation of drinking or enhancement of early alcohol use have focused on the role of stress associated with social interactions or rearing conditions. For example, the emotional stress of intermittent social separation during adolescence appears to increase alcohol consumption in adulthood, as demonstrated in rhesus monkeys (Kraemer and McKinney 1985). Studies in rhesus monkeys also show that maternal separation (for the first 6 months of life) increases the amount of alcohol consumed by offspring (Higley et al. 1991). In rats, early social separation (Schenk et al. 1990) or subordinate social status can induce alcohol drinking (Blanchard et al. 1987). Studies in mice have demonstrated that after social hierarchies are established, fight-stressed submissive mice exhibit increased alcohol consumption (Hilakivi-Clarke and Lister 1992). In addition, alcohol self-administration in mice can be increased by a psychological stressor—a signal that predicts exposure to an aversive noise stimulus (Mollenauer et al. 1993).

Investigation in rats of the relationship between types of stress and the motivation to drink alcohol has found that stress from chronic isolation, but not stress caused by immobilization, increased alcohol consumption. This observation suggests that stress associated with the social environment may be a critical parameter in alcohol-seeking behavior (Roske et al. 1994). Roske et al. (1994) also compared the effects of stress associated with being raised in isolation and stress associated with immobilization on both alcohol intake and *opioid* release in rats. They observed that being reared in isolation did not stimulate opioid release but increased alcohol intake; in contrast, stress resulting from immobilization activated the opioid system and did not increase alcohol consumption. Thus, not all types of stress increase alcohol consumption, and effects on the opioid system may be a primary factor in determining whether a stressor increases alcohol consumption (Roske et al. 1994).

Stress associated with the social environment may be a critical parameter in alcohol-seeking behavior.

These studies indicate that both adverse rearing environments and prolonged exposure to social stress or social isolation are potential determinants of abnormal alcohol drinking. Such findings in animals are important for understanding environmental factors, such as family structure and child-rearing practices, that may enhance the risk for developing drinking problems or alcohol dependence in humans (Tarter et al. 1984). Identifying changes in neuroendocrine function that are associated with environmental stressors through future studies may be useful for detecting people who are at risk for developing alcohol problems and for developing pharmacologic treatments that can counteract these disturbances before the onset of alcohol abuse.

Conditioned Preference Models

Conditioned preference tasks provide an alternative approach to the study of alcohol-seeking behavior. These tasks involve assessment of the rewarding value of alcohol by examining the degree to which animals seek or avoid an environment (place preference vs. place avoidance) or a flavor (taste preference vs. taste avoidance) that has been paired with alcohol on previous occasions. These procedures rely on environmental stimuli that induce motivational states indicative of alcohol-seeking behavior while the animal is not under the influence of the drug. In rats, after a single pairing of alcohol with an environmental or taste stimulus, alcohol more often induces conditioned aversion than preference (Asin et al. 1985; Cunningham 1979; Horowitz and Whitney 1975; Risinger and Cunningham 1992). However, repeated exposure to alcohol attenuates the aversive actions of alcohol (Gauvin and Holloway 1992; Stewart et al. 1991) and can result in conditioned place preference (Bozarth 1990; Reid et al. 1985). These results suggest that tolerance develops to the aversive effects of alcohol and is an important factor leading to the acceptance, and possibly abuse, of the drug.

In addition, an inherited reduced sensitivity to the aversive effects of alcohol may contribute to genetically determined alcohol preference. Taste aversion to alcohol is both stronger and more persistent in NP rats than in P rats (Froehlich et al. 1988); however, both strains show similar degrees of alcohol-induced place aversion (Schechter 1992). Thus, in P rats, genetic factors appear to account for reduced sensitivity to some but not other aspects of alcohol's aversive properties.

In contrast, several strains of mice develop a clear preference for environments associated with alcohol's actions (Cunningham et al. 1993). This effect is strongest when animals are placed in an alcohol-associated environment only for a short time after injection of alcohol (Cunningham and Prather 1992), an interesting observation in that alcohol has stimulatory *psychomotor* effects in the early phase but not in the later phase after administration. These findings support the hypothesis that the activating locomotor effects of many drugs are linked to their pleasurable rewarding effects and, in many cases, predict liability for their abuse.

Approaches for Studying Anxiolytic Properties of Alcohol

The acute effects of alcohol consumption include stress-reducing, anxiolytic actions that have been documented in humans and several animal models of anxiety. These actions combined with the mood-elevating effects of alcohol may contribute to alcohol's rewarding and reinforcing effects and, ultimately, to alcohol abuse. In addition, alcohol withdrawal produces anxiety, which can persist for months after abstinence. From a motivational point of view, then, relief of anxiety associated with alcohol withdrawal may contribute to negative reinforcing (i.e., anxiety-alleviating) properties of alcohol that may perpetuate alcohol abuse.

Researchers have used several behavioral models to study alcohol's anxiolytic effects. A common procedure involves exposing animals to some conflict that generates approach-avoidance behavior. For example, when operant responding for a reinforcing stimulus such as food is occasionally punished by delivery of an aversive electrical shock, the animal's response to the reinforcing stimulus normally becomes suppressed. This behavioral suppression can be reversed by anxiolytic drugs such as benzodiazepines.

A second behavioral test used to study anxiety is the elevated plus maze. Rats or mice are placed on a plus sign-shaped maze that is elevated above the ground. Two arms of the maze are protected by barriers (closed arms), while the remaining two arms are unprotected (open arms) and leave the animal exposed. Animals typically prefer to spend most of their time in the closed arms of the maze, but exposure to anxiolytic compounds dramatically increases the amount of time an animal spends in the open arms. In contrast, *anxiogenic* drugs or conditions associated with anxiety, such as alcohol withdrawal, reduce the amount of time an animal will remain in the open arms. The plus maze test is an established method for predicting the anxiolytic or anxiogenic effects of drugs or environmental as well as physiologic conditions.

Anxiolytic properties of alcohol provide another potential mechanism contributing to alcohol abuse or dependence.

A third behavioral test, the social interaction test, takes advantage of the observation that normal social interactions are suppressed when rats are placed in an unfamiliar and brightly lit environment. Under these conditions, anxiolytic drugs markedly increase social interactions.

Similar to classic anxiolytic drugs, alcohol has antianxiety effects in both the elevated plus maze (Lister 1987; Pellow and File 1986) and the social interaction test (File 1980; Lister and Hilakivi 1988). Alcohol can effectively reverse behavioral suppression in the conflict test; however, in contrast to benzodiazepines, animals rapidly develop tolerance to this effect of alcohol (Koob and Britton 1996). Collectively, these observations suggest that the anxiolytic properties of alcohol provide another potential mechanism contributing to alcohol abuse or dependence and that clarification of the neurobiological bases of alcohol's anxiolytic effects may be essential to understanding alcohol addiction. Indeed, much of the recent work involving animal models of anxiety has been concerned with the exploration of receptor systems in the brain that mediate alcohol's effect on anxiety. These studies are discussed in the corresponding sections below.

Drug Discrimination Procedures

The subjective effects of alcohol, which include its euphoric and anxiolytic effects, can be studied by using drug discrimination procedures. In these procedures, animals are trained to make a certain response when they recognize the presence of alcohol and a different response when they cannot recognize exposure to alcohol. When the alcohol-exposed animal is then given a new drug, which it cannot distinguish from alcohol, it will respond as it would for alcohol. Drug discrimination procedures can be used to evaluate the degree to which drugs known to activate or block specific neurotransmitter *receptors* in the brain are perceived as similar to or are capable of attenuating the subjective effects of alcohol. In such tests, the use of drugs that can fully or partially substitute for or block the stimulus effects of alcohol allow identification of neurochemical systems that mediate these stimulus effects. Drug discrimination experiments cannot be used to directly demonstrate reinforcing properties of alcohol, but they can provide critical information about neurobiological mechanisms that may participate in the rewarding effects of alcohol.

Results from studies using drug discrimination tests indicate that alcohol's subjective effects are not mediated by a single neurotransmitter receptor but depend on the combined activation of several different receptor classes (Grant and Barrett 1991*b*; Grant et al. 1991; Kubena and Barry 1969; Overton 1977). Thus, alcohol can be viewed as a "mixed" internal stimulus consisting of several components that overlap with, but are not identical to, those of various other sedative hypnotic drugs. One recent study has confirmed that different receptors mediate such effects but that these receptors appear to be differentially sensitive to alcohol, depending on the dose of alcohol that the animal was trained to recognize (Grant and Colombo 1993*b*). As discussed later in this chapter, these drug discrimination tests have identified neurotransmitter receptors that mediate alcohol's intoxicating effects and in the future may contribute to the development of specifically targeted pharmacotherapies that alter or block certain behavioral effects of alcohol.

Neuropharmacology of Alcohol's Neurobehavioral Effects

As discussed above, alcohol's subjective effects involve multiple neurotransmitter systems and their receptors. Similarly, it has become increasingly clear that, in contrast to many other drugs of abuse which activate specific neurotransmitters or interact with specific receptors, the pharmacologic properties that support alcohol reward and alcohol-seeking behavior involve multiple neurotransmitter and neurochemical messenger systems (figures 1 and 2).

Dopamine

The neurotransmitter dopamine plays a central role in the "hedonic," or pleasurable, effects of many drugs of abuse and in the reinforcing effects of nondrug stimuli, such as food or electrical stimulation of the brain. A shared property of many commonly abused drugs, such as psychomotor stimulants (e.g., cocaine and amphetamine) and opiate drugs (e.g., morphine and heroin), is their ability to enhance dopamine neurotransmission in the *nucleus accumbens* (Di Chiara and Imperato 1988). Destruction of dopamine nerve terminals in the nucleus accumbens by administration of a neurotoxin and treatment with pharmacologic agents that block dopamine receptors abolish the self-administration of cocaine and

Figure 1. Schematic representation of the involvement of neurochemical, genetics, and environmental factors in the reward profile of alcohol.

Many different neurotransmitter systems and hormones are involved in the mediation of the pharmacologic effects of alcohol. Understanding how and to what extent these neurochemical signals contribute to or regulate alcohol consumption is one of the many challenges faced by alcohol researchers. The reward profile has been likened to an orchestra in which alcohol is the conductor and each neurochemical is an instrument that plays a "reward tune." But only when all instruments are playing together will the full "reward symphony" be experienced. Adding to this complexity, the final pharmacologic and subjective effect of alcohol is determined by factors related to the individual, such as genetic background, sociocultural determinants, hormonal status, age, and gender.

"Reward" Profile of Alcohol

Central Nervous System Stimulation	Euphoria	Preference	Tension Reduction	Sedation	Muscle Relaxation
DA* NA OP ACh EAA	DA NA OP	5-HT DA	GABA EAA	GABA	GABA

Individual
Factors Influencing Sensitivity to Alcohol

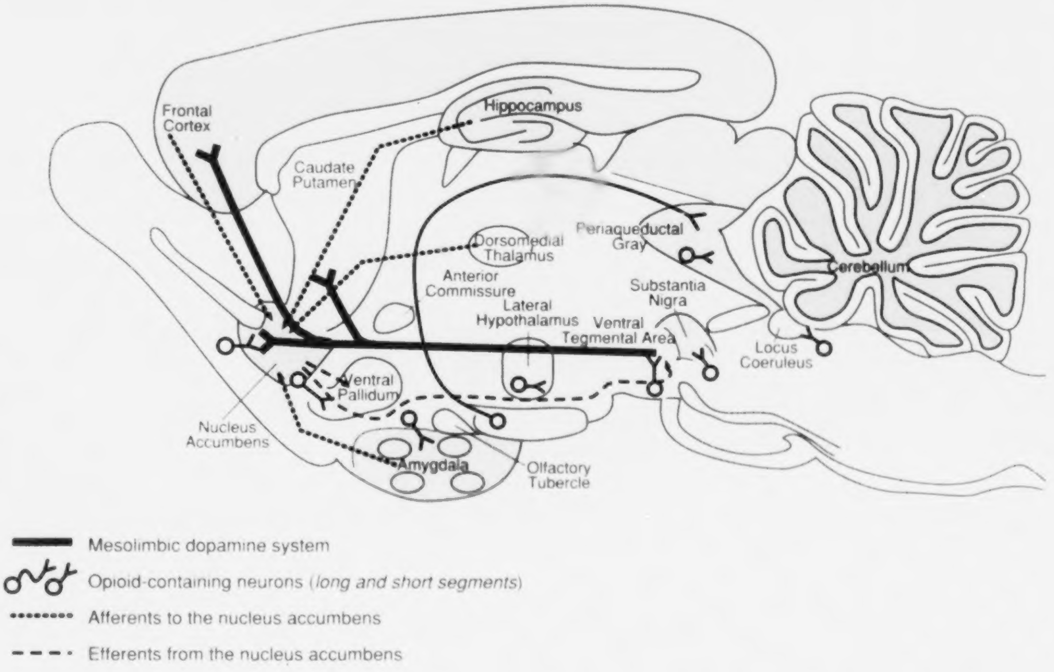
Genetic Age Hormonal Environmental

*DA = dopamine, NA = noradrenaline, OP = opioids, ACh = acetylcholine, EAA = excitatory amino acids (i.e., glutamate), 5-HT = serotonin, GABA = γ-aminobutyric acid.

Source: Engel et al. 1992. Reprinted by permission.

Figure 2. Section of the rat brain illustrating several neurochemical systems prominently implicated in the rewarding and dependence-inducing effects of alcohol and other drugs of abuse.

The mesolimbic dopamine system originates in the midbrain ventral tegmental area and projects to the nucleus accumbens, frontal cortex, olfactory tubercle (*pathway not shown*), and regions of the caudate putamen. Opioid-containing neurons mediate opiate reward, dependence, and withdrawal and also have been implicated in alcohol preference and reinforcement. The opioid peptide systems consist of the local enkephalin circuits (*short segments*) and the hypothalamic midbrain ß-endorphin circuit (*long segment*). Afferents to the nucleus accumbens originate in the limbic system (hippocampus, amygdala) and in the frontal cortex and dorsomedial thalamus. Efferents from the nucleus accumbens thought to be involved in the rewarding properties of alcohol and other drugs extend to the ventral pallidum and ventral tegmental area. Stippling reflects the distribution of GABA_A receptors thought to contribute to the CNS depressant effects of alcohol.


Frontal Cortex
Hippocampus
Caudate Putamen
Dorsomedial Thalamus
Periaqueductal Gray
Cerebellum
Anterior Commissure
Lateral Hypothalamus
Substantia Nigra
Ventral Tegmental Area
Locus Coeruleus
Ventral Pallidum
Nucleus Accumbens
Amygdala
Olfactory Tubercle
Mesolimbic dopamine system
Opioid-containing neurons (*long and short segments*)
Afferents to the nucleus accumbens
Efferents from the nucleus accumbens

Source: Koob 1992. Adapted from Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Sciences* 13(5):177–184, 1992, by permission.

opiates by interfering with the neuronal circuitry necessary to mediate the reinforcing effects of these drugs (see Koob et al. 1987 for a review).

Studies using pharmacologic manipulations of dopamine neurotransmission in rats that self-administer alcohol implicate dopamine in the rewarding actions of alcohol as well. Systemic administration of dopamine *antagonists*, compounds that block the effects of this neurotransmitter at its receptor, substantially decreases alcohol consumption. In operant procedures, where alcohol availability is contingent upon the performance of a lever press response, animals treated with prototypical dopamine antagonists (e.g., haloperidol and pimozide) begin responding for alcohol normally but cease responding shortly thereafter (Pfeffer and Samson 1985, 1988). This rapid termination in responding suggests that dopamine antagonists interfere with alcohol's ability to enhance dopamine neurotransmission and thereby reduce the ability of alcohol to act as a reinforcer.

Administration of dopamine *agonists*, compounds that increase the activity of dopamine systems, also can inhibit alcohol intake (Pfeffer and Samson 1985, 1988; Weiss et al. 1990). However, unlike dopamine antagonists, dopamine agonists (e.g., d-amphetamine and apomorphine) do not accelerate the cessation of responding for alcohol in rats but instead produce behavioral disruptions that result in slowed, sporadic response patterns accompanied by reduced alcohol consumption (Pfeffer and Samson

1985, 1988). One possible explanation for these results is that because dopamine agonists themselves potently activate dopamine neurotransmission, alcohol may not provide sufficient additional stimulation to act as a reinforcer. In other words, the already heightened hedonic state produced by dopamine agonists may suppress the motivation to respond for alcohol and, in effect, make further alcohol ingestion redundant.

The presumed interaction of alcohol with dopamine systems has been confirmed in biochemical and physiologic studies showing that alcohol activates dopamine *neurons* in the midbrain (Brodie et al. 1990) and enhances the release of dopamine in the nucleus accumbens to which these neurons project (Imperato and Di Chiara 1986; Wozniak et al. 1991; Yoshimoto et al. 1991). The role of dopamine in the reinforcing actions of alcohol has been corroborated and extended by investigations of alcohol's actions on dopaminergic brain "reward regions." In these studies, either alcohol or drugs that interact with dopamine receptors are microinjected directly into the brain. Responding for alcohol is suppressed by direct infusion of dopamine antagonists into the nucleus accumbens, a treatment that interferes with dopamine neurotransmission, and by injection of a dopamine agonist into the *ventral tegmental area*, a treatment that inhibits activity of dopamine neurons (Hodge et al. 1993*a*; Rassnick et al. 1992; Samson et al. 1993). Thus, interfering with alcohol-stimulated dopamine activity at dopamine's brain sites of action reduces alcohol intake. These findings have been complemented by studies showing that rats will perform operant responses to receive injections of a weak alcohol solution directly into the ventral tegmental area (Gatto et al. 1994). Alcohol's reinforcing properties appear to be sufficiently robust in these animals to impart conditioned reinforcing properties on environmental stimuli, in that an alcohol-associated environmental stimulus (an illuminated house light) could, by itself, maintain alcohol-seeking behavior. This finding points to a possible role of ventral tegmental dopamine neurons in the motivation to obtain alcohol (Gatto et al. 1994).

Other studies show that direct self-administration of alcohol and anticipation of alcohol access (in the absence of alcohol) enhance dopamine release in the nucleus accumbens (Weiss et al. 1993). Thus, in addition to its role in direct reinforcing properties of alcohol, dopamine release may contribute significantly to the initiation of behaviors directed at acquiring alcohol and to craving for alcohol[2] (figures 3 and 4). Consistent with this possibility, in detoxified alcoholic patients, the dopamine antagonist haloperidol decreased craving and difficulty in resisting additional alcohol consumption induced by a "priming dose" of alcohol (Modell et al. 1993).

Studies in rodents selectively bred for high alcohol consumption have contributed to understanding inherited aspects of dopamine's role in alcohol preference and reward. For example, compared with NP and LAD rats, P and HAD rats show significant reductions in dopamine content in the nucleus accumbens (see Li et al. 1994 for a review). Despite this forebrain dopamine deficiency, mesolimbic dopamine mechanisms (figure 2) in alcohol-preferring rat strains are more sensitive to dopamine-activating and dopamine-reinforcing effects of alcohol. Alcohol stimulates dopamine release more effectively in P rats during self-administration than in rats not selected for alcohol preference (Weiss et al. 1993). Enhanced *dopaminergic* sensitivity to alcohol also has been demonstrated in another line of rats selectively bred for alcohol preference (Fadda et al. 1989), and Wistar rats selected for high alcohol preference show greater dopamine release than rats of the same strain that avoid alcohol (Engel et al. 1992). Furthermore, P rats but not NP rats self-administer dopamine into the ventral tegmental area (Gatto et al. 1994). Finally, in P and HAD rats, but not in NP or LAD rats, alcohol stimulates locomotor activity. Locomotor activation is associated with enhanced mesolimbic dopamine activity and is thought to reflect the rewarding properties of a drug (Krimmer and Schechter 1992; Waller et al. 1986; Wise and Bozarth 1987). Together, these data support the hypothesis that inherited deficits in brain dopamine content and hyperreactivity of mesolimbic dopamine transmission in response to alcohol contribute to genetically determined alcohol preference (Cloninger 1987; McBride et al. 1990).

Dopamine also has been implicated in the aversive and dysphoric effects of alcohol withdrawal; the alleviation of these effects by alcohol may reinforce continued alcohol consumption in dependent persons. In rats chronically exposed to alcohol, substantial deficiencies in accumbal dopamine release are observed after removal of alcohol. Indeed, Schulteis et al. (1996) recently reported that alcohol-dependent rats undergoing withdrawal will perform lever press responses for alcohol in an apparent attempt to alleviate withdrawal symptoms (Schulteis et al. 1996). Alcohol self-administration at the peak of

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[2] Craving for alcohol is a hunger for the drug often experienced by recently abstinent alcoholics and is an important determinant of relapse to drinking.

Figure 3. Illustration of an operant alcohol self-administration procedure with simultaneous monitoring of neurotransmitter release in the brain by intracranial microdialysis.

(LEFT) Shown is a male alcohol-preferring (P) rat trained to press one of two levers for access to a 10-percent alcohol solution or water. Responding at each lever initiates delivery of 0.1 ml of fluid (alcohol or water) into a receptacle positioned in the center of the operant chamber. (RIGHT) Illustration of the microdialysis method that involves implantation of a thin hollow dialysis fiber into a brain region of choice. Neurochemicals in the extracellular space, such as neurotransmitters released at nerve terminals, diffuse across the dialysis membrane (*arrows*), where they can be recovered for analysis. This technique also permits direct application of substances such as alcohol into the brain and allows the local neurochemical effects of such substances to be monitored. Studies using these techniques have provided many insights about the neurobiological basis of alcohol's effects on brain reinforcement systems. For example, such studies have shown that alcohol stimulates the release of the reward-associated neurotransmitter dopamine; that this effect varies with genetic and gender differences; that dopamine release can occur in response to the mere expectation of access to alcohol; and that the effects of alcohol on dopamine release are modulated by another neurotransmitter, serotonin, that has been linked to genetically determined alcohol preference.

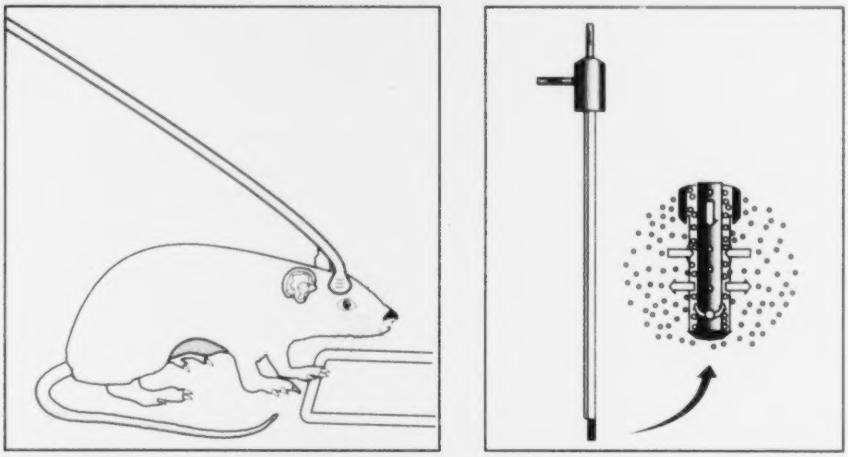
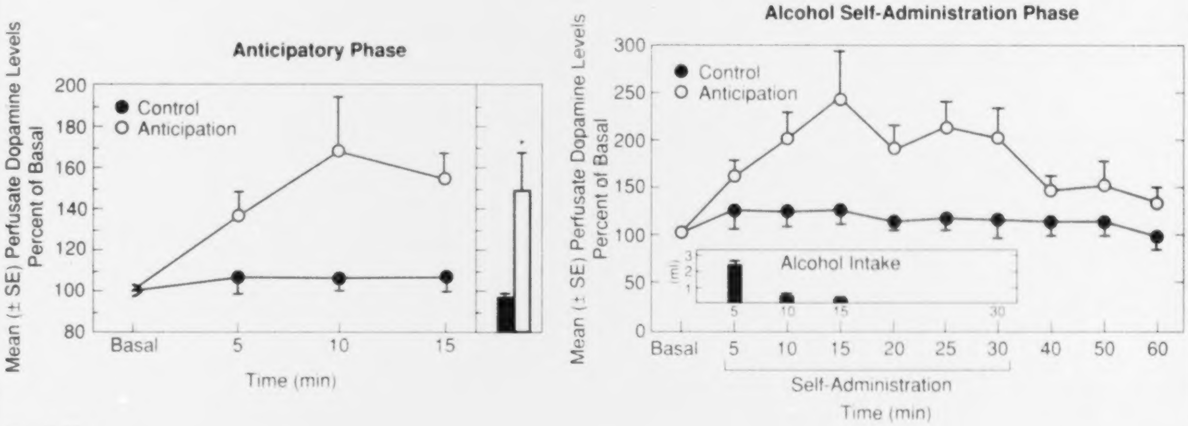


Figure 4. Effects of anticipation of access to alcohol and subsequent oral alcohol self-administration on dopamine release in the nucleus accumbens of alcohol-preferring (P) rats.

The figure shows dopamine concentrations measured by intracranial microdialysis in the nucleus accumbens before, during, and after a 30-minute operant self-administration. The amounts (ml) of 10% alcohol (w/v) ingested per 5-minute interval are represented in the bar graph inset. Dopamine release increased during an anticipatory phase before alcohol availability. Dopamine levels rose again as a result of alcohol self-administration and reached peak levels 10–15 minutes after peak alcohol intake. Administration of a nondrug reinforcer (saccharin) had no effect on the release of dopamine (data not shown).



*$p < 0.05$.

Source: Weiss et al. 1993. Adapted by permission.

withdrawal reversed the withdrawal-associated dopamine deficiency and returned dopamine levels in the nucleus accumbens to prewithdrawal levels. These findings suggest that dopamine neurotransmission plays a role not only in the acute, positive reinforcing actions of alcohol but also in the negative reinforcing properties of alcohol in dependent rats (Weiss et al. 1994).

In spite of growing evidence in favor of a dopaminergic mediation of alcohol reward, in most, but not all (Quarfordt et al. 1991), recent (Lyness and Smith 1992; Rassnick et al. 1993*c*) and earlier (Kiianmaa et al. 1979) work, chemical denervation of the nucleus accumbens failed to alter voluntary alcohol intake. Combined with the pharmacologic and biochemical data above, these results suggest that although mesolimbic dopamine transmission is associated with important aspects of alcohol reinforcement, it is not critical in this regard, and other neurochemical systems participate in the mediation of alcohol's reinforcing actions.

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) has long been implicated in the control of alcohol-seeking behavior. This role of serotonin has been established in numerous studies in which pharmacologic manipulations that increase the synaptic availability of this neurotransmitter suppressed alcohol intake. For example, drugs that increase the extraneuronal concentration of serotonin by inhibiting its reuptake[3] reduce alcohol consumption in humans and reverse alcohol preference in animals (Sellers et al. 1992; see Naranjo and Bremner 1994 and George in press for reviews). Alcohol itself stimulates the release of 5-HT in limbic brain regions, as might be expected from the suppression of alcohol intake observed with treatments that increase serotonin activity (Yoshimoto et al. 1991, 1992).

Other evidence linking serotonin to alcohol abuse comes from studies using rodent lines genetically selected for alcohol preference, nonpreference, or aversion. Many of the alcohol-preferring rodent lines exhibit marked differences in brain serotonin content compared with lines selected for alcohol nonpreference or aversion. In particular, P and HAD rats (see Li et al. 1994 for a review), when compared with their NP and LAD counterparts, exhibit reductions in serotonin content in several brain regions as well as other significant abnormalities in brain serotonin systems (Gongwer et al. 1989; Murphy et al. 1987). P rats in comparison with NP rats have fewer serotonin neurons in several regions of the forebrain and show differences in the density of serotonin receptor populations (McBride et al. 1993, 1994; Zhou et al. 1993). These reductions in serotonergic innervation predominate in brain areas responsible for drug reinforcement, emotion, memory, and temperature regulation (Zhou et al. 1993). All of these processes are directly related to the intake of alcohol or its physiologic and behavioral effects, indicating that reductions in serotonin neurons may reflect a loss of regulatory control by brain serotonin systems over brain neuronal circuitries that control the rewarding or aversive actions of alcohol.

That impaired serotonin function contributes to alcohol abuse and dependence is also suggested by evidence of deficient serotonin synthesis, turnover, or receptor function in many alcoholic patients (Ballenger et al. 1979; Lee and Meltzer 1991; Linnoila et al. 1983; Thomson and McMillen 1987). Further evidence comes from recent studies in chronic alcoholics documenting a severe loss of serotonin neurons in the midbrain and reduced serotonin uptake in several brain regions (Chen et al. 1991; Halliday et al. 1993). In agreement with animal studies discussed above, treatment of human alcoholics with various serotonin reuptake inhibitors decreases alcohol consumption (see Naranjo and Bremner 1994 and Sellers et al. 1992 for reviews).

Interestingly, abnormalities in brain serotonin function in humans also have been implicated in depressive illness, a condition that often co-occurs with alcoholism (Regier et al. 1990). In a recent study, Cornelius et al. (1993) demonstrated significant improvements on measures of both alcohol intake and depression in suicidally depressed alcoholics after 8 weeks of treatment with fluoxetine, a serotonin uptake inhibitor. Thus, it is possible that serotonin uptake inhibitors have therapeutic potential because they ameliorate symptoms of depression and reduce alcohol intake.

Clinical and laboratory studies in humans also have provided intriguing data in favor of a role for serotonin in the intoxicating and subjective effects of alcohol. In detoxified alcoholic patients, drugs that act as partial agonists at serotonin receptors produce a sensation of feeling "high" and a craving for alcohol (Benkelfat et al. 1991; Lee and Meltzer 1991). Krystal et al. (1994) used detailed questionnaires and rating scales to evaluate the stimulus effects of one of these compounds, m-chlorophenylpiperazine (MCPP), and confirmed that MCPP produced a high that was perceived as "alcohol-like." In addition, MCPP induced nervousness, anger, alcohol craving, and the subjective feeling that "alcohol would reduce discomfort." These data confirm findings from animal studies that implicate serotonin systems in the discriminative stimulus properties of alcohol (Grant and Barret 1991*b*; Signs and Schechter 1988). The elicitation of alcohol craving by MCPP also confirms an alcohol-like effect because the drug would act similarly to a priming dose of alcohol, which can stimulate alcohol craving. It is also interesting to note that this study was conducted in type II alcoholics, who often exhibit symptoms of antisocial personality disorder with an increased likelihood of violence during intoxication (Cloninger 1987).

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[3] Neurotransmitter reuptake is a regulatory mechanism that helps to control neurotransmitter function.

Abnormalities in brain serotonin function in humans also have been implicated in depressive illness, a condition that often co-occurs with alcoholism.

In recent years, much research has been directed toward identifying the specific serotonin receptor subtypes that regulate alcohol consumption. These studies have shown that agonists of one type of serotonin receptor, 5-HT$_{1A}$, and antagonists of other serotonin receptors, 5-HT$_2$ and 5-HT$_3$, reduce alcohol intake in rodents (Chen et al. 1992; Fadda et al. 1991; Hodge et al. 1993*b*; Knapp and Pohorecky 1992; Knapp et al. 1992; Schreiber et al. 1993). Preliminary clinical data indicate that a 5-HT$_3$ receptor antagonist (ondansetron) can reduce alcohol intake in humans, and a 5-HT$_2$ antagonist (ritanserin) reduced the desire to drink but had no effect on alcohol intake (Naranjo et al. 1995; Toneatto et al. 1991). In addition to identifying pharmacologic agents that reduce alcohol intake and craving, these studies indicate differential actions of various receptor subtypes in regulating alcohol consumption.

The precise roles of these receptor types in control of alcohol intake remain to be established, although research has implicated interactions with the dopamine reward system and anxiolytic effects of serotonin receptor agonists and antagonists. For example, 5-HT$_3$ receptor antagonists that reduce alcohol intake also suppress the alcohol-induced release of dopamine in the nucleus accumbens (Campbell and McBride 1995; Yoshimoto et al. 1991), block the anxiolytic effects of alcohol (Grant and Barrett 1991*a*), and attenuate subjective effects of alcohol in animals (Grant and Barrett 1991*b*) and humans (Johnson et al. 1993). Observations in macaque monkeys have suggested that abnormal alcohol ingestion is associated with heightened anxiety and that 5-HT$_{1A}$ agonists act primarily to reduce anxiety which in turn decreases alcohol consumption (Collins and Myers 1987). Similarly, 5-HT$_{1A}$ agonists suppress alcohol intake in rats housed under conditions that heighten anxiety (Wilde and Vogel 1994).

Serotonin receptors also have been implicated in alcohol withdrawal. 5HT$_{1A}$ agonists suppress and can reverse the anxiogenic behavioral effects of alcohol withdrawal in rats (Lal et al. 1991). Lal et al. (1993) also have observed that blocking 5-HT$_{1C}$ and 5-HT$_2$ receptors with a single large dose of an antagonist prevents the anxiogenic effects of alcohol withdrawal, as measured in the elevated plus maze test, for up to 7 days after treatment. In a subsequent study, these researchers determined that chronic alcohol exposure in rats results in an increased sensitivity to the anxiogenic effects of a 5-HT$_{1C}$ agonist administered during alcohol withdrawal (Rezazadeh et al. 1993). The 5-HT$_{1C}$ receptor, therefore, is likely to play a significant role in alcohol withdrawal-associated anxiety, and drugs capable of specifically blocking 5-HT$_{1C}$ receptors may prove beneficial in the treatment of alcohol withdrawal symptoms (Rezazadeh et al. 1993).

Amino Acid Neurotransmitters

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is an inhibitory amino acid neurotransmitter that mediates its effects through specific GABA receptors (see chapter 3 for a discussion of this neurotransmitter and its receptors). GABA$_A$ receptors may play a significant role in the reinforcing actions of alcohol. Alcohol has behavioral effects similar to those of several anxiolytic agents, including benzodiazepines and barbiturates, which exert their actions through binding to one type of GABA receptor, the GABA$_A$ receptor. Alcohol also shares discriminative stimulus properties with these drugs (Grant and Colombo 1993*b*; Shelton and Balster 1994; York 1978). Thus, it is possible that some of alcohol's behavioral effects are mediated through GABA receptors.

To investigate this possibility, researchers have examined the extent to which ligands that interact with different sites of the GABA$_A$ receptor complex modify alcohol-mediated behaviors. In particular, studies with benzodiazepine *inverse agonists*—agents that block the effects of benzodiazepines and exert effects that are exactly opposite to those of these anxiolytic agents—have provided strong indirect support for a role of the GABA$_A$ receptor complex in the rewarding actions of alcohol. One such inverse agonist, RO 15-4513, has been shown to suppress alcohol intake in animal experiments involving both free access to alcohol (McBride et al. 1988) and operant procedures (Samson et al. 1989). In the former study, suppression of alcohol intake was blocked by a benzodiazepine antagonist, thus implicating the benzodiazepine site of the GABA$_A$ receptor in the effects of RO 15-4513 (McBride et al. 1988). Similar studies have examined the effects of RO 15-4513 and another benzodiazepine inverse agonist, FG 7142, on alcohol intake (June et al. 1994*a,b*; Rassnick et al. 1993*a*). In free-drinking and operant self-administration situations, the inverse agonists suppressed alcohol intake (June et al. 1994*b*; Rassnick et al. 1993*a*). However, when the benzodiazepine antagonist flumazenil was coadminstered with RO 15-4513, alcohol intake was suppressed but only at very high doses (June et al. 1994*b*). Thus, the role of the benzodiazepine binding site of the GABA$_A$ receptor in alcohol intake remains to be determined.

In related studies, a convulsant agent that also binds the GABA$_A$ receptor strongly inhibited responding for alcohol, suggesting that interactions with a convulsant-sensitive site of the GABA$_A$ receptor complex may also contribute to the reinforcing actions of alcohol. Interestingly, the convulsant agent, as well as RO 15-4513, is more effective at reversing alcohol intake in NP rats than in P rats (McBride et al. 1988; Rassnick et al. 1993*a*). This observation is consistent with genetic differences in brain GABA systems between these rat lines; for example, compared with NP rats, P rats have a greater density of GABA-containing neurons in the nucleus accumbens (Hwang et al. 1990). Overall, these experiments provide strong support for a role of GABA$_A$ receptors in alcohol reinforcement and indicate that differences in *GABAergic* innervation or function may contribute to alcohol preference in selectively bred animal models.

Studies exploring the mechanisms by which alcohol exerts its anxiolytic effects, which are a critical aspect of its reinforcing properties, also implicate the GABA$_A$ receptor complex. Certain GABA antagonists and inverse agonists reverse the anxiolytic effects of alcohol in conflict tests, as reflected by their interference with the reinstatement of operant responding by alcohol (Koob et al. 1986; Liljequist and Engel 1984). Similarly, in the elevated plus maze test, RO 15-4513 reversed the alcohol-induced increase in time that the rats spent on the open arms, indicating that this compound blocked the anxiolytic actions of alcohol (Lister 1988; Prunell et al. 1994). A recent study by Criswell et al. (1994) compared the effects of alcohol and a benzodiazepine agonist (chlordiazepoxide) on performance of rats in the elevated plus maze test. These investigators found that behavior patterns indicative of alcohol's anxiolytic effects closely parallel those produced by chlordiazepoxide, suggesting a role of the GABA$_A$ receptor in alcohol's anxiolytic effects.

Some reinforcing actions of alcohol are not mediated through the GABA$_A$ receptor. RO 15-4513, for example, had no effect on alcohol-induced taste aversion or conditioned place preference (June et al. 1992; Risinger et al. 1992). These effects may thus involve other neurotransmitter systems, such as brain dopamine systems. Characterization of alternate brain mechanisms and receptors involved in reinforcement is an area of active study.

Glutamate

The amino acid glutamate is the brain's major excitatory transmitter, and alcohol can inhibit this excitatory action by acting at glutamate receptors. Of several glutamate receptor subtypes, the NMDA[4] receptor appears to be the most sensitive to alcohol's effects. Given the ability of alcohol to inhibit the stimulatory effects of glutamate and to enhance the inhibitory effects of GABA, it is not surprising that the range of alcohol-related behaviors associated with the NMDA receptor is similar to that involving the GABA$_A$ receptor.

Several NMDA antagonists have anxiolytic, subjective, and reinforcing effects that resemble those of alcohol, suggesting a role for NMDA receptors in mediating these behavioral effects. Researchers have shown in several animal species that alcohol shares the discriminative stimulus properties of noncompetitive NMDA antagonists, which block glutamate's actions by blocking the passage of *ions* through the receptor's ion channel (Grant and Colombo 1993*a*; Sanger et al.

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[4] NMDA—*N*-methyl-D-aspartate—binds to, and has been used to distinguish, NMDA receptors from other glutamate receptor subtypes (see chapter 3 for a discussion of glutamate receptor subtypes).

1993). In contrast, competitive NMDA antagonists, which block glutamate's binding to the NMDA site of the receptor, do not consistently show substitution in rats trained to discriminate alcohol (Grant and Colombo 1993*a*; Sanger 1993; Shelton and Balster 1994). The congruence between the stimulus effects of the noncompetitive class of NMDA antagonists and alcohol not only complement biochemical studies showing that alcohol antagonizes NMDA-mediated glutamate neurotransmission but also suggest that alcohol itself may act as a noncompetitive NMDA antagonist (Grant 1994).

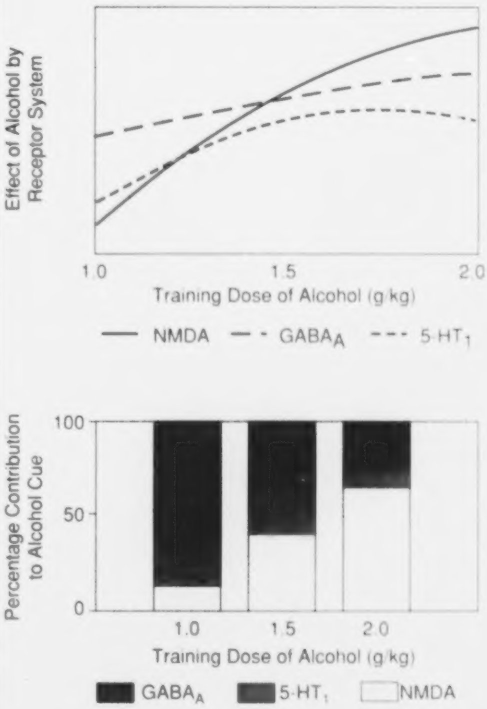
As mentioned earlier, subjective effects of alcohol include euphoric and anxiolytic properties that contribute to reinforcement of alcohol-seeking behavior. Numerous studies have implicated NMDA receptors in alcohol reinforcement (Grant 1994). One recent study has found that responding for alcohol in operant procedures was reduced after injection of a competitive NMDA antagonist into the nucleus accumbens (Rassnick et al. 1992). In view of the important role of dopamine in mediating the rewarding effects of alcohol, this observation suggests an interaction of NMDA mechanisms and dopamine neurotransmission in the nucleus accumbens in producing alcohol's positive reinforcing effects.

Because important subjective effects of alcohol also are mediated by the $GABA_A$ receptor, researchers believe that the pharmacologic events underlying these effects are mediated by both GABA and glutamate neurotransmission. Shelton and Balster (1994) have compared alcohol's effects with those of GABA agonists and NMDA antagonists in drug discrimination protocols. Their findings for NMDA antagonists were discussed earlier. Of the GABA agonists tested, barbiturate and benzodiazepine $GABA_A$ receptor agonists yielded the greatest degree of substitution for alcohol; however, none of these substances could fully substitute for alcohol. This incomplete degree of substitution indicates the involvement and perhaps the interaction of the GABA and NMDA receptors in producing the unique stimulus properties of alcohol.

Related experiments have further clarified alcohol's complex discriminative stimulus effects and the significance of NMDA and other receptors in mediating these effects (Grant and Colombo 1993*b*). In drug discrimination tests, the relative contribution of different receptor systems was found to depend on the dose of alcohol that animals were trained to recognize (figure 5). Stimulus effects related to activation of 5-HT_1 receptors prevailed when low alcohol doses were used as training doses. As the training dose of alcohol was increased, the animals based their recognition of alcohol on stimulus effects similar to those of the $GABA_A$ agonist pentobarbital. With high training doses of alcohol, stimulus effects of alcohol resembled those of a noncompetitive NMDA receptor antagonist. At intermediate doses, the animals were able to recognize activation of all three receptor systems as similar to

Figure 5. Hypothetical representation of the proportional contribution of $GABA_A$, serotonin 5-HT_1, and glutamate NMDA receptors to the subjective (discriminative stimulus) effects corresponding to different doses of alcohol.

Perceived similarity of alcohol with drugs selectively acting on each of these three receptor systems changes as a function of the alcohol dose that animals were trained to recognize. These data illustrate that the subjective effect of alcohol is "mixed" in that it consists of several components mediated by various receptor systems that are differentially sensitive to the actions of alcohol.



Source: Grant and Colombo 1993*b*. Reprinted by permission of the publisher, from Pharmacological analysis of the mixed discriminative stimulus effects of ethanol. *Alcohol Alcohol* (Suppl. 2):445–449. Copyright 1993 by Elsevier Science Inc.

the effects of alcohol (Grant and Colombo 1993*b*). Therefore, the relative contribution of different receptor systems to the subjective effects of alcohol depend on the reference dose of alcohol and are not amplified uniformly when the dose of alcohol is increased.

Neuropeptides and Peptide Neuromodulators

Opioids

Opioid peptides, which act on the same receptor as opiate drugs, are potent reinforcers that are readily self-administered by animals. Alcohol promotes the synthesis and release of the opioids beta-endorphin and met-enkephalin in the brain and pituitary gland (De Waele et al. 1992; Reddy and Sarkar 1993; see Gianoulakis 1989 for a review). Under a wide range of drinking conditions in rats and monkeys, antagonists that block the binding of opioids to their receptors produce an often long-lasting reduction in alcohol intake (Altshuler et al. 1980; Froehlich et al. 1987; Hubbell et al. 1991; Myers et al. 1986; Schwarz-Stevens et al. 1992; Volpicelli et al. 1986). The release of these peptides is stimulated shortly after alcohol ingestion, when BAC is low, and inhibited at later time points as BAC increases (Gianoulakis 1989). This release profile corresponds to the biphasic action of alcohol, characterized by euphoric and anxiolytic effects at low doses and depressive and aversive effects at higher doses. Activation of the opioid system by alcohol represents yet another mechanism by which the drug exerts its reinforcing effects.

These findings indicate that opioid systems play a prominent role in the development of the desire to consume alcohol, and opiate antagonists may be particularly useful for the treatment of this condition.

The opiate antagonist naltrexone (Trexan®, ReVia®) was recently shown to be of significant benefit in the treatment of alcoholism when used in combination with intensive behavioral therapy (O'Malley et al. 1992; Volpicelli et al. 1992; also see Chapter 10, Treatment of Alcoholism and Related Problems). In detoxified male alcoholics, this comprehensive drug-plus-therapy treatment decreased the number of drinking episodes, frequency of relapse, and craving for alcohol. The reduction in craving may occur because blocking opiate receptors may reduce the effects of stimuli that normally elicit craving rather than (or in addition to) interfering directly with the reinforcing effects of alcohol. Several animal studies have examined the mechanisms by which opiate antagonists decrease alcohol consumption (Cunningham et al. 1995; Hyytiä and Sinclair 1993; Schwarz-Stevens et al. 1992). These studies have shown that a single injection of an opiate antagonist does not affect the initial motivation to obtain alcohol in operant procedures but reduces alcohol intake once drinking has begun (Hyytiä and Sinclair 1993; Schwarz-Stevens et al. 1992). A progressive decline in drinking occurred when opiate antagonist treatment was repeatedly paired with access to alcohol over consecutive days, and alcohol intake often remained suppressed after the experiment was terminated (Hyytiä and Sinclair 1993). These results indicate that opiate antagonists attenuate the hedonic value of alcohol after it is consumed, an action that eventually appears to produce extinction of alcohol-seeking behavior.

An experiment by Cunningham et al. (1995) further explored this possibility. These researchers treated mice with the opiate antagonist naloxone before repeated pairings of alcohol with a distinct environment and found that the antagonist did not interfere with the development of conditioned place preference. However, when naloxone was administered for the first time just before place-preference testing, it interfered with the expression of preference by shortening the time animals spent in the alcohol-associated environment. These results suggest that alcohol's direct rewarding effects do not depend on activation of opioid receptors; rather, maintenance of alcohol-conditioned place preference, which reflects alcohol-seeking behavior and perhaps alcohol craving, may be mediated via opioid receptors. These findings indicate that opioid systems play a prominent role in the development of the desire to consume alcohol, and opiate antagonists may be particularly useful for the treatment of this condition.

Several experiments have sought to identify the opiate receptor types involved in modifying alcohol intake. Traditional opiate antagonists, such as naltrexone, nonselectively block all opioid receptors and have general inhibitory effects on appetitive or consummatory behavior, including the consumption of sweets, food, and water (Reid 1985; Schwarz-Stevens et al. 1992; Weiss et al. 1990). However, it is possible that naltrexone suppresses alcohol intake by acting on a specific receptor type. Studies designed to identify opiate receptor types that confer specific aspects of alcohol's reinforcing actions indicate that antagonists which react selectively with certain opioid receptor subtypes (the mu and delta opioid receptors) can reduce alcohol intake (Froehlich et al. 1991; Hyytiä 1993; Krishnan-Sarin et al. 1995*b*). Like traditional opiate antagonists, however, selective mu and delta opioid receptor blockers also can inhibit the consumption of food and sweets.

To date, no opiate receptor exclusively associated with alcohol reward has clearly been identified (Hawkins et al. 1992; Krishnan-Sarin et al. 1995*b*). However, studies with novel antagonists for a newly identified opioid receptor, the delta$_2$ opioid receptor subtype, have shown that blockade of this receptor suppresses alcohol intake independent of the palatability of alcohol, a factor known to influence alcohol intake (Krishnan-Sarin et al. 1995*a*). Thus, the delta$_2$ opioid receptor may be a candidate for a selective mediation of alcohol's rewarding effects. The identification of such a receptor may be critical for the development of opiate antagonists that act exclusively at this receptor and have increased efficacy but fewer potential side effects than traditional opiate antagonist drugs.

Perhaps interactions among neurotransmitters in the nucleus accumbens can be viewed as orchestrating the rewarding effects of alcohol.

Opioid systems also may contribute to the reinforcing actions of alcohol by interacting with the dopamine system. As mentioned earlier, alcohol stimulates the release of dopamine in the nucleus accumbens, and dopamine antagonists suppress alcohol drinking. Alcohol may activate the dopaminergic reward circuitry via an action on endogenous opioid systems. Accumulating evidence suggests that the stimulation of dopamine release by alcohol is, in part, mediated by opioid peptides: Both naltrexone and a selective delta opioid receptor antagonist have been shown to prevent alcohol-induced dopamine release (Acquas et al. 1993; Benjamin et al. 1993). Thus, the clinical efficacy of opiate antagonists may lie in their ability to block the reinforcing aspects of alcohol that depend on dopaminergic and nondopaminergic actions of opioid peptides.

The modification of alcohol-induced dopamine release in the nucleus accumbens by opioid peptides illustrates the presumed interactive nature of multiple neurotransmitter systems in mediating the rewarding properties of alcohol. Interactions relevant to alcohol's reinforcing actions appear to exist among dopamine, glutamate, and serotonin neurotransmission in the nucleus accumbens. The nucleus accumbens receives neuronal projections containing glutamate, serotonin, and opioids from the limbic and midbrain regions that play a role in motivational and emotional processes. Perhaps interactions among these neurotransmitters in the nucleus accumbens can be viewed as orchestrating the rewarding effects of alcohol by organizing functional output from this structure (Koob et al. 1994*b*).

Corticotropin-Releasing Factor

Corticotropin-releasing factor (CRF), which is a peptide, is crucial for regulating the body's responses to stress (see Chapter 5, Effects of Alcohol on Health and Body Systems, for a more detailed description of CRF). Physical demands, psychological distress, or adaptive behavioral changes initiate a cascade of neuroendocrine events that ultimately result in the release of adrenal hormones, which have widespread effects on metabolic and immunologic processes. The activation of this system, commonly referred to as the "hypothalamic-pituitary-adrenal axis" (HPA) in reference to the brain structures and endocrine glands involved, is controlled by the release of CRF from the ***hypothalamus***. CRF also appears to mediate stress-related responses by modulating pathways in the central nervous system involved in the regulation of ***autonomic*** activity and in emotional responses to stress (see Fisher 1989 and Koob 1994*a* for reviews).

In laboratory animals, administration of CRF produces a variety of behavioral effects typical of stress. CRF also has anxiogenic actions in several behavioral tests of anxiety, an effect that is reversed by benzodiazepines and by alcohol, suggesting an interaction between CRF and the GABA$_A$ receptor complex (see Koob et al. 1994*a* for a review).

Some studies indicate that alcohol may affect stress reactions through actions within the HPA axis. Acute alcohol intake activates the HPA axis by enhancing CRF release from neurons in the hypothalamus (Redei et al. 1988). Similarly, chronic exposure to alcohol increases CRF gene expression and synthesis of CRF in the hypothalamus (Rivier et al. 1990). Activation of the HPA axis and increases in emotionality that resemble the effects of stress during alcohol withdrawal also have been described (De Soto et al. 1985; Freund 1969; Tabakoff et al. 1978). Ehlers et al. (1992) noted that P rats showed an enhanced electroencephalographic response to CRF administration compared with NP rats, an observation that is consistent with findings that P rats are more "anxious" in behavioral tests of anxiety (Stewart et al. 1993). Thus, a relationship may exist between alcohol preference, CRF status, and responsivity to stress.

Chronic alcohol administration also can elevate CRF levels in brain regions outside the hypothalamus (George et al. 1990). CRF, therefore, may play a role in alcohol dependence that is independent of its role in the HPA axis. For example, recent studies suggest that CRF mechanisms in the *amygdala*, a brain structure involved in emotional processes, play a prominent role in the anxiogenic effects of alcohol withdrawal. Direct injection of the CRF antagonist, alpha helical CRF, into the amygdala completely reversed withdrawal-associated anxiety, as measured in the elevated plus maze test (Rassnick et al. 1993*b*). A role for CRF in the amygdala was further confirmed by intracranial microdialysis where it was found that the local extracellular levels of the peptide increased progressively by more than 500 percent in rats undergoing alcohol withdrawal (Pich et al. 1995). Thus, discrete extrahypothalamic CRF systems may be affected by chronic exposure to alcohol, and overactivity of these systems may contribute to distress observed during withdrawal.

Vasopressin

Arginine vasopressin (AVP) is a neurochemical messenger produced in the hypothalamus that regulates water reabsorption in the kidney. AVP also acts through brain receptors to influence physiologic functions, such as cardiovascular regulations, and neurobehavioral processes, such as arousal, learning, and memory. AVP also has been implicated in the development of tolerance to alcohol based on studies in AVP-deficient rats, which fail to develop or show abbreviated tolerance to some of alcohol's physiologic effects (Pittman et al. 1982). The role of AVP in tolerance has been confirmed by studies in which administration of vasopressin enhanced the development of tolerance (Rigter et al. 1980). Moreover, once developed, tolerance is maintained by vasopressin administration even in the absence of further alcohol ingestion (Hoffman et al. 1978; Wu et al. 1994). Development of tolerance appears to involve a brain AVP receptor known as V_1, in that administration of a specific V_1 receptor antagonist can accelerate the loss of tolerance (Szabó et al. 1988). Furthermore, genetic preference for alcohol has been correlated with AVP function in studies showing that a selectively bred strain of alcohol-preferring rats (AA rats) display substantially greater tolerance to alcohol and also secrete more vasopressin from the pituitary than do alcohol-nonpreferring ALKO Nonalcohol rats (ANA) (Linkola et al. 1977). In mice, differential vasopressin responsiveness to chronic alcohol exposure also has been implicated as a factor in strain-dependent differences in alcohol tolerance (Ebel et al. 1991).

These findings suggest that chronic consumption of alcohol may influence the development of tolerance through alterations in brain AVP synthesis or release; however, studies examining this issue have yielded mixed results. Because administration of exogenous AVP enhances the development of tolerance (Rigter et al. 1980), chronic alcohol exposure might be expected to increase synthesis or plasma levels of AVP. Indeed, chronic alcohol treatment increases plasma AVP levels in mice (Hoffman and Dave 1991). However, the same treatment in rats decreases plasma AVP levels, and in both species, chronic alcohol exposure decreases hypothalamic AVP synthesis (Gulya et al. 1993; Hoffman and Dave 1991; Ishizawa et al. 1990; Sanna et al. 1993). Researchers suggest that the development of tolerance does not require increased synthesis of AVP and that decreased AVP synthesis may help maintain constant levels of the neurochemical messenger (Gulya et al. 1993). Thus, the role of hypothalamic AVP synthesis in tolerance requires further research.

Some evidence suggests that the actions of vasopressin in tolerance involve brain sites other than the hypothalamus. Recent studies have implicated the *septal area*, which contains a high density of V_1 receptors (Giri et al. 1990). In rats, vasopressin stores in the septal area are regulated by gonadal hormones and decrease dramatically after castration. Depletion of septal AVP by castration can disrupt the development of tolerance in these animals (McGivern et al. 1993). AVP-mediated tolerance to alcohol may also involve serotonergic mechanisms (see Hoffman et al. 1990*a* for a review). Evidence to support this hypothesis comes from a recent study in which chemical lesions of serotonin terminals in the septal area and *hippocampus* abolished the capacity of exogenous AVP to maintain tolerance (Wu et al. 1994). The effectiveness of AVP was restored by continuous infusion of serotonin or selective serotonin 5-HT_2 and 5-HT_3 agonists, thus implicating receptor systems in alcohol tolerance that also mediate the subjective and reinforcing actions of alcohol.

Studies showing that vasopressin can interfere with the acquisition of heroin and cocaine self-administration suggest that the effects of this neuropeptide also may impact processes related to alcohol-maintained reinforcement. This possibility is supported by studies in which a vasopressin analog, desglycinamide-(Arg^8)-vasopressin (DGAVP), was found to inhibit the acquisition of voluntary alcohol intake in rhesus monkeys (Kornet et al. 1992). The mechanisms by which vasopressin participates in alcohol reinforcement are unclear. However, a recent demonstration that AVP *potentiates* the acute intoxicating effects of alcohol in rats (as measured in a motor performance task) through actions on V_1 receptors suggests that AVP enhances the aversive effects of alcohol and thereby inhibits alcohol intake (Wu et al. 1992).

Neuroactive Steroids

A new area of research concerning alcohol's behavioral actions focuses on a group of endogenous steroids known as neurosteroids. These substances are called neurosteroids because they are synthesized in the brain from cholesterol, a steroid precursor, or as metabolites of *gonadal steroids* or *mineralocorticosteroids*. Neurosteroids have a fast action on neuronal membranes when compared with the slow, delayed effects of traditional steroids.

Neurosteroids modulate the activity of GABA by binding to a specific recognition site at the $GABA_A$ receptor complex (Majewska et al. 1986; Morrow et al. 1990). Some neurosteroids, such as the progesterone metabolite allopregnanolone and $3\alpha,5\alpha$-tetrahydrodeoxycorticosterone (THDOC), act as agonists at the $GABA_A$ receptor complex to produce neuronal inhibition and behaviorally to exert hypnotic and anxiolytic effects (Bitran et al. 1991; Crawley et al. 1986; Wieland et al. 1991). Other neurosteroids, such as pregnenolone sulfate and dehydroepiandrosterone (DHEA), act as antagonists at the $GABA_A$ receptor to produce increased neuronal excitability; they also can produce anxiogenic and proconvulsant effects in behavioral tests (Majewska and Schwartz 1987; Majewska et al. 1990; Melchior and Ritzman 1994*b*).

That both alcohol and neurosteroids act on the $GABA_A$ receptor complex suggests that alcohol's behavioral effects may involve interactions with neurosteroids or that neurosteroids may influence alcohol-seeking behaviors. Consistent with this possibility, allopregnanolone and THDOC have been shown to share sedative and anxiolytic discriminative stimulus properties with alcohol (Ator et al. 1993). Neurosteroids also act through $GABA_A$ receptors to potentiate or reverse the anxiolytic actions of alcohol as measured in the elevated plus maze test (Melchior and Ritzman 1994*a,b*), enhance the hypnotic effects of alcohol (Melchior and Ritzman 1992), and attenuate seizure susceptibility during alcohol withdrawal (Devaud et al. 1995). These data support interactions with $GABA_A$ receptors as prominent mechanisms behind alcohol's behavioral effects.

Neurosteroids also act at the NMDA receptor complex. Pregnenolone sulfate can enhance the physiologic and behavioral effects of glutamate at the NMDA receptor (Bowlby 1993; Maione et al. 1992; Wu et al. 1991), whereas allopregnanolone interferes with glutamate effects at the NMDA receptor (Smith 1991). Considering the findings of GABA-mediated neuronal inhibition by allopregnanolone, as discussed above, these results suggest that allopregnanolone acts in a manner similar to alcohol on both receptor systems. In contrast, pregnenolone sulfate exerts actions opposite to those of alcohol at both receptors.

Researchers are just beginning to understand the precise interactions between neurosteroids and alcohol. The discovery of these endogenous modulators of GABA and NMDA function and their unique binding site at the $GABA_A$ receptor complex provides new perspectives and tools for the investigation of mechanisms by which alcohol exerts its behavioral actions and for the development of novel compounds that selectively antagonize acute or chronic effects of alcohol.

Gender Differences

Several studies have established that the drinking habits of women are different from those of men (Blume 1991; Mercer and Khavari 1990). For example, men are more likely than women to consume alcohol and to be heavy drinkers (Dawson and Archer 1992). Gender differences in alcohol consumption patterns traditionally have been attributed to social and cultural factors, but it is also possible that alcohol affects males and females differently. For example, given the same dose of alcohol, women attain higher BACs than men (Frezza et al. 1990). In addition, women may be more sensitive to adverse consequences of chronic alcohol abuse: The development of alcohol dependence and associated health problems, such as alcohol-associated brain and liver damage, progresses more rapidly in women than in men (Farid and Clarke 1992; Hanna et al. 1992; Harper and Kril 1990; Norton et al. 1987).

The development of systematic methods and animal models to identify mechanisms behind these gender differences is in its infancy. To date, research implicates pharmacokinetic factors (Mezey et al. 1992); dimorphic neurochemical responsivity of brain reward systems to alcohol (Blanchard et al. 1993a); and differences in the modulation of brain neuronal activity by gonadal hormones, including the so-called neurosteroids, in the divergent alcohol intake patterns and sensitivity to alcohol between the sexes (Devaud et al. 1995; Rivier 1993; see Lancaster 1994 for a review).

Many studies of gender differences in rodent models of alcohol self-administration show that, in contrast to humans, females drink significantly more alcohol than do males (Adams et al. 1991; Blanchard et al. 1993*a*; Lancaster and Spiegel 1992). However, in one of these studies, despite their greater alcohol intake, BACs of female rats were no higher than those of male rats (Lancaster and Spiegel 1992). Behavioral studies also have documented gender differences in alcohol's effects. Middaugh et al. (1992) have shown that female mice are less responsive than males to low-dose stimulatory actions of alcohol, an effect that was unrelated to differences in BACs. While some researchers report a higher rate of "first-pass" gastric alcohol metabolism in female compared with male rats (Mezey et al. 1992), others find this route of alcohol metabolism to be negligible in the rat (Smith et al. 1992). Thus, differences in gastric metabolism cannot readily account for gender differences in alcohol intake and responsiveness to its effects. Instead, it seems that the reduced sensitivity of female rodents to alcohol's behavioral and intoxicating actions may contribute to the increased voluntary alcohol intake by these animals.

Studies exploring neurobiological mechanisms behind gender differences in rodents indicate that despite their reduced sensitivity to alcohol, female rats have a heightened neurochemical responsiveness relative to male rats in terms of alcohol-induced dopamine release in the nucleus accumbens (Blanchard et al. 1993*a*). The latter effect is enhanced by prenatal exposure to alcohol (Blanchard et al. 1993*b*). As outlined above, activation of dopamine neurotransmission in this brain region is associated with the hedonic, reinforcing actions of many drugs of abuse and alcohol. It is therefore possible that a functional relationship exists between enhanced alcohol-stimulated dopamine release and the greater voluntary alcohol intake of female rats. The gender-related difference in alcohol-induced dopamine release was specific to the mesolimbic dopamine reward pathway and did not occur in another forebrain area containing dopamine nerve terminals that is not directly involved in the reinforcing actions of alcohol (Blanchard et al. 1993*a*). These findings point toward a gender difference in the neurochemical response to alcohol by a select population of dopaminergic neurons that mediate the reinforcing actions of alcohol.

Mankes et al. (1991) have explored hormonal contributions to gender-specific differences in alcohol consumption in rats by examining differences in prenatal hormone exposure resulting from in utero sibling contiguity. (In utero sibling contiguity refers to the intrauterine position of males relative to females, e.g., a male positioned between two females or a female positioned between two males.) Mankes et al. found that positioning of a male between two females in utero can alter alcohol consumption patterns such that in adulthood, drinking patterns of the male resemble those of females. The precise mechanism by which gonadal hormones modify alcohol consumption is unclear; however, alcohol intake patterns in adult female rats vary significantly over the course of the estrous cycle (Forger and Morin 1982). Thus, the responsiveness of neural systems regulating voluntary alcohol intake may be driven in part by circulating levels of gonadal hormones.

Steroid hormone functions and neurosteroid functions are thought to contribute to gender differences in alcohol's effects (Lancaster 1994). Supportive evidence for these mechanisms comes from several studies. For example, female rats release more corticosterone in response to alcohol than males do, an effect that is associated with higher BACs (Rivier 1993). Female rats also have higher levels in brain and plasma of the neurosteroid 3α-5α-THP (3α-hydroxy-5α-pregnan-20-one), which possesses anxiolytic and anticonvulsant activity (Corpéchot et al. 1993; Purdy et al. 1991). The presence of higher levels of this neurosteroid in female rats is interesting in light of studies showing that females also have higher thresholds for convulsant-induced seizures than males (Kokka et al. 1992). Other researchers have observed a greater sensitivity of female rats to the anticonvulsant effects of 3α-5α-THP during alcohol withdrawal (Devaud et al. 1995). These data indicate that 3α-5α-THP attenuates seizure susceptibility during alcohol withdrawal, a property that can perhaps be exploited therapeutically.

Alcohol and Aggression

Alcohol use has been linked to aggression and violence in humans. These behaviors likely involve multiple interacting neurobiological, genetic, social, cultural, and other determinants (see Chapter 7, Effects of Alcohol on Behavior and Safety). For reasons that are not clear, some individuals are more susceptible than others to the aggression-enhancing actions of alcohol. Many people who consume large quantities of alcohol have no tendency to engage in violent behavior, and many clinical and experimental observations in humans and animals indicate that doses of alcohol that induce aggression in some individuals also can reduce aggression in others.

In nearly all animal species, there is great variation in aggressive responses to alcohol. Some of this variability may be related to dose effects. Typically, low doses rather than high doses of alcohol induce aggression in animal models (see Berry 1993 and Miczek et al. 1994 for reviews). However, attempts to identify behavioral and environmental predictors of alcohol-induced aggression in several species have so far identified only one characteristic, social dominance, as a predictor of heightened aggression after consumption of proaggressive alcohol doses. The relationship between social dominance and susceptibility to alcohol-induced aggression appears to involve elevated levels of testosterone (Miczek et al. 1992; Winslow et al. 1988).

Both direct and indirect evidence suggests an association between alcohol-induced aggression and brain serotonergic mechanisms.

One strategy for identifying neurobiological systems alcohol acts upon has focused on animal models of alcohol-exaggerated but "natural" adaptive forms of aggression (e.g., defense of territory or rival fighting among males). In general, alcohol (particularly at low doses) can exaggerate offensive aggression in these animal models (Blanchard et al. 1993*a*; Miczek et al. 1992). The neurobiological mechanisms responsible for this effect appear to involve mechanisms similar to those that mediate many other behavioral effects of alcohol.

For example, $GABA_A$ receptor antagonists reverse the aggression-inducing effect of low alcohol doses in rats and squirrel monkeys. This effect appears to be selective for the proaggressive actions of alcohol because $GABA_A$ antagonists had no effect on the reduction in aggression observed with high alcohol doses (Weerts et al. 1993). Conversely, some $GABA_A$ agonists can augment the proaggressive actions of alcohol in animals (Miczek and O'Donnell 1980) and as shown in a recent study of human behavior, can potentiate alcohol-related aggression and feelings of hostility in heavy social drinkers (Bond and Silveira 1993).

Both direct and indirect evidence suggests an association between alcohol-induced aggression and brain serotonergic mechanisms. Several treatments that increase the availability of serotonin in the brain suppress alcohol-induced attack behavior in mice elicited by a shock to the foot or by placement of an intruding mouse in a resident mouse's home cage (Wagner et al. 1993). Serotonin has long been thought to be essential to impulse control; in support of this hypothesis, low concentrations of serotonin metabolites are found in the cerebrospinal fluid of certain violence-prone individuals (Asberg et al. 1976; Everett 1961). More specifically, a profile of impulsive violence appears associated with low serotonin metabolite concentrations in humans (Virkkunen et al. 1994). In animals, aggressive behavior directed against intruding rivals also is attenuated by activation of serotonin receptors, in particular by agonists of the 5-HT_1 receptor (see Miczek et al. 1993 for a review). The prevention of alcohol-induced aggression by pharmacologic elevation of extraneuronal serotonin in the brain therefore seems to support serotonin deficiency as an underlying factor in the proaggressive actions of alcohol. However, this association is far from established, in part because alcohol itself can enhance the release of serotonin in several brain regions. Clearly, additional research is needed to understand the significance of the serotonin and other neurotransmitter and neuroendocrine systems in the proaggressive effects of alcohol.

Alcohol Effects on Learning and Memory

Chronic alcohol abuse in conjunction with deficient nutrition can result in neuropsychological impairments such as difficulties with attention, intellectual memory, concept shifting, abstract thinking, and problem solving (Bowden and McCarter 1993; Grant 1987; Lishman 1990; Tarter and Parsons 1971). These deficits, particularly compromised abstraction and problem-solving skills, appear to be associated with atrophy and reduced metabolic function in the frontal region of the cerebral cortex (Adams et al. 1993; Samson et al. 1986). Alcohol interferes with memory and learning processes after chronic abuse, and even acute alcohol exposure impairs recall of information learned during intoxication (Mungas et al. 1994; Ryback 1971). Alcohol appears to impair consolidation of new information, possibly through inhibitory effects on NMDA receptors that result in blockage of long-term potentiation (LTP) (Lister et al. 1987), a process that likely plays a critical role in the formation of new memories (Hoffman et al. 1990*b*; see discussion of LTP in chapter 3).

The nature of alcohol's interference in cognitive functions has been examined in research using animal models of memory and learning. With respect to acute effects of alcohol, a primary interest is whether observed alcohol-related detriments derive specifically from impaired learning processes or impaired memory formation. In a behavioral test that allows effects on memory to be determined separately from effects on learning, Melchior et al. (1993) have demonstrated that low doses of alcohol impair behavior-dependent memory in mice (Melchior et al. 1993). Because low doses of alcohol, as used in this experiment, also inhibit LTP, this finding further suggests that alcohol acutely impairs memory, possibly through blockade of LTP.

Biochemical studies of chronic alcohol consumption and memory deficits have demonstrated an association between these deficits and reductions in the neurotransmitter acetylcholine in the hippocampus and frontal cortex; pharmacologic treatments that increased extraneuronal levels of acetylcholine reversed these memory deficits (Beracochea et al. 1992). Similar data show that transplants of acetylcholine-rich fetal brain tissue improve alcohol-induced impairments in spatial memory of rats (Hodges et al. 1991). Similarly, in rats with memory deficits induced by chronic exposure to alcohol, intracortical grafts of glial tissues enhanced cholinergic (acetylcholine-mediated) function and produced an almost complete recovery in working memory (Brückner and Arendt 1992). The reversal of cholinergic deficits was attributed to *neurotrophic factors* present in the graft that stimulated cholinergic activity. Together, these data suggest that memory deficits induced by chronic exposure to alcohol arise from the failure of retrieval processes that are dependent on the functional integrity of cholinergic neurotransmission.

Summary

Our knowledge of the brain structures and functions affected by alcohol has expanded significantly in recent years. With this knowledge has come a greater understanding of the links between alcohol-induced brain changes and alcohol-induced behavioral changes.

Sophisticated methods and animal models have been used to study alcohol-seeking behavior and the environmental and genetic forces that motivate and reinforce drinking. Animals have been selectively bred for alcohol preference or nonpreference and used in specially designed behavioral approaches, such as operant models, conflict tests, and drug discrimination procedures.

For example, scientists have used operant procedures, in which animals can obtain alcohol only by performance of a specific task, to study the "cost" of alcohol as an environmental influence on alcohol intake. These experiments have shown that the amount of alcohol consumed can be modified by its cost, defined as the amount of work required to obtain the drug, regardless of genetic preference for alcohol. In addition, this study revealed an association between genetic predisposition for high alcohol intake and a greater motivation to work for alcohol.

Conflict tests, in which animals trained to respond to alcohol as a reinforcing stimulus are occasionally punished (e.g., by the administration of an electric shock), have been used to study the anxiety-reducing properties of alcohol. This treatment normally suppresses responding to the stimulus, but exposure to alcohol has been shown to reduce anxiety and reverse behavioral suppression. With continued alcohol exposure, however, animals rapidly became tolerant to alcohol's anxiolytic effects. Conflict tests and similar behavioral strategies have shown that the stress-reducing actions of alcohol likely reinforce its continued use and contribute to the development of alcohol dependence.

Drug discrimination procedures determine the ability of animals trained to recognize alcohol to distinguish between alcohol's subjective effects (such as its anxiolytic and euphoric effects) and those of other psychotropic drugs. In such tests, identification of drugs that can fully or partially substitute for alcohol, together with knowledge of the neurotransmitter systems affected by those drugs, can help characterize the brain pathways that mediate the behavioral effects of alcohol. Studies using drug discrimination procedures have shown that alcohol's subjective effects are not mediated by any one neurotransmitter or neurotransmitter receptor but depend on the combined actions of multiple neurotransmitter systems.

Among the many neurotransmitters characterized as mediators of alcohol-related behaviors are dopamine, serotonin, GABA, opioids, glutamate, and a new class of compounds known as neurosteroids. Dopamine, which mediates the pleasurable effects of many drugs, has been strongly implicated in the reinforcement of alcohol-seeking behaviors. This role has been confirmed in operant procedures that have identified the nucleus accumbens and the ventral tegmental area as specific brain regions where alcohol activates dopamine transmission and presumably influences responding for alcohol and the amount of alcohol consumed. Dopamine also has been implicated in the aversive effects of alcohol withdrawal. For example, alcohol-dependent animals undergoing withdrawal will self-administer alcohol in an apparent attempt to alleviate withdrawal symptoms; furthermore, alcohol restores a withdrawal-associated dopamine deficiency observed in these animals. Collectively, these findings suggest that dopamine contributes to alcohol's positive and negative reinforcing properties.

The actions of serotonin have long been associated with alcohol-seeking behavior in experimental animals and in humans. In regions of the brain implicated in drug reinforcement, selectively bred alcohol-preferring rats compared with their alcohol-nonpreferring counterparts have reduced serotonin content and fewer serotonin neurons. In humans, alcoholism is associated with a loss of serotonin neurons and deficiencies in serotonin synthesis, turnover, and receptor function. Moreover, similar to findings in laboratory animals, treatment of alcoholics with pharmacologic agents that increase serotonin availability in the brain can reduce alcohol consumption in these individuals. Recent investigations have characterized several serotonin receptor subtypes ($5HT_3$, $5HT_2$, and $5HT_{1A}$) as participants in the control of alcohol intake.

Receptors for the inhibitory neurotransmitter GABA are thought to play critical roles in the reinforcing actions of alcohol. Alcohol has anxiolytic effects that resemble those of benzodiazepines, agents that act through the A-type GABA receptor ($GABA_A$), suggesting that this pharmacologic property of alcohol is mediated through $GABA_A$ receptors. Studies of alcohol's stress-reducing effects have implicated $GABA_A$ receptors, in that certain $GABA_A$ receptor antagonists—compounds that block or reverse GABA's actions at $GABA_A$ receptors—can reverse the anxiolytic effects of alcohol in conflict tests.

Similarly, receptors for the excitatory neurotransmitter glutamate appear to participate in alcohol reinforcement. Antagonists for one type of glutamate receptor, the NMDA receptor, have subjective and reinforcing effects that resemble those of alcohol. Drug discrimination tests have shown that noncompetitive NMDA receptor antagonists, which block ion flux through the receptor's ion channel, have stimulus properties similar to alcohol, whereas competitive NMDA receptor antagonists, which block glutamate's binding to the NMDA receptor, can only partially substitute for alcohol. These results suggest that alcohol may interfere with NMDA receptor function by acting as a noncompetitive NMDA receptor antagonist.

A new line of research explores the role of neurosteroids, compounds that bind to and modulate the activity of both $GABA_A$ receptors and NMDA receptors. Several neurosteroids have been characterized. Some produce neuronal inhibition via the $GABA_A$ receptor to produce anxiolytic and hypnotic effects. Others act as GABA receptor antagonists to increase neuronal excitability and can thereby induce anxiety and convulsions. Different neurosteroids also can enhance or interfere with the physiologic and behavioral effects of glutamate at the NMDA receptor. Neurosteroids may interact with alcohol to influence alcohol-seeking behavior. For example, different neurosteroids may enhance or reverse the anxiolytic actions of alcohol. Researchers have just begun to characterize these interactions in investigations that may aid development of novel pharmacotherapeutic agents.

These various neurotransmitters can act together to produce behavioral changes associated with alcohol use. Alcohol is thought to stimulate or inhibit numerous neurotransmitter activities simultaneously in producing its rewarding and reinforcing effects. For example, interactions among alcohol, serotonin, and dopamine are suggested in experiments showing that $5HT_3$ antagonists can reduce alcohol intake and dopamine release in the nucleus accumbens. Similarly, alcohol produces its rewarding properties, in part, by activating dopamine release through actions on opioid peptides such as endorphins and enkephalins. Naltrexone and another opiate antagonist that interacts selectively with the delta opioid receptor have been shown to prevent alcohol-induced dopamine release. Thus, the clinical efficacy of opiate antagonists may lie, in part, in their ability to block the reinforcing effects of alcohol that depend on dopaminergic mechanisms in the brain.

In humans and in experimental animals, alcohol use has been linked with aggression and violent behavior. Some people are susceptible to alcohol's proaggressive properties, while others are not, for reasons that are not clearly understood but likely involve genetic, social, neurobiological, and other determinants. Studies of alcohol-induced aggression in animals have indicated the involvements of various neurotransmitter systems. For example, GABA$_A$ receptor antagonists block aggression induced by low alcohol doses in rodents. Serotonin also has been implicated in the control of violent behavior. In mice, treatments that increase availability of serotonin in the brain reduce aggression. Because alcohol itself can increase brain levels of serotonin, however, the role of this neurotransmitter in alcohol-induced aggression remains uncertain.

Chronic alcohol use may cause neuropsychological deficits in learning and memory. Alcohol appears to impair the consolidation of newly acquired information, possibly through effects on NMDA receptors that participate in long-term potentiation, a process thought to be critical to memory formation. Biochemical studies of memory deficits that occur with chronic alcohol consumption have associated these deficits with reductions in brain levels of the neurotransmitter acetylcholine. In rodents, transplants of acetylcholine-rich fetal brain tissue have been shown to improve alcohol-induced memory impairments. Thus, alcohol-related memory deficits appear to involve disruption of glutamate and acetylcholine pathways, but the precise mechanisms behind these deficits require further investigation.

This overview highlights recent progress in understanding how the diverse behavioral effects of alcohol may be coupled to specific alcohol-induced changes in the brain. Studies involving selectively bred animals, advanced behavioral analyses, and newly developed bioanalytical methods have provided important information about many neurochemical pathways in which alcohol interacts and which appear to be responsible for maintaining the motivation to drink. Continued research aimed at identifying brain regions, receptor types, and interactive effects of neurotransmitter systems affected by alcohol are needed to clarify the neuropharmacologic basis of alcohol abuse and dependence. This information will accelerate the development of pharmacologic agents designed to modify neuronal mechanisms and functions of critical brain regions that participate in alcohol abuse and dependence.

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Chapter 5

Effects of Alcohol on Health and Body Systems

Introduction

Alcohol can cause harm to virtually every tissue and organ in the body. Drinking can lead to various consequences, depending on factors such as the amount of alcohol consumed, gender, age, and nutritional status. Because the liver receives portal blood directly from the intestines, it takes the brunt of high alcohol concentrations, and as the primary site of alcohol metabolism, it forms abundant toxic alcohol metabolites. Thus, liver damage may be among the most serious consequences of alcohol abuse. Alcohol also may cause damage to the heart and can elevate blood pressure; heavy alcohol consumption can increase the risk for heart failure and stroke. Excessive alcohol consumption can injure nervous tissues, producing diverse neuropsychological impairments and interfering with hormonal regulation of a variety of cellular and metabolic activities. Chronic alcohol exposure also impairs immune functions that protect against infection. Recent advances in elucidating the direct and indirect roles of alcohol in causing damage to these various body systems are detailed in this chapter.

Alcohol-Induced Liver Injury

Alcohol abuse is the leading cause of liver-related mortality in the United States. Excessive alcohol consumption leads to two serious types of liver injury: In some instances it causes hepatic inflammation (alcoholic hepatitis), and in others it induces progressive liver scarring (*fibrosis*[1] or *cirrhosis*). Frequently, alcoholic hepatitis and fibrosis co-occur in the same individual (Chedid et al. 1991). The exact prevalence of alcoholic liver disease in the United States is difficult to assess because alcohol consumption is often underreported, but current health statistics suggest that the number of people suffering some form of alcoholic liver disease likely exceeds 2 million (Dufour et al. 1993). An estimated 900,000 people have cirrhosis, and of the 26,000 who die each year, at least 40 percent and perhaps as many as 90 percent have a history of alcohol abuse (Dufour et al. 1993).

Several factors are involved in the development of alcoholic liver disease. Prolonged alcohol consumption is of obvious importance. Epidemiologic studies suggest that a "threshold" dose of alcohol must be consumed, amounting to a cumulative dose of 600 kilograms[2] for men and between 150 and 300 kilograms for women, for liver injury to become apparent (Lelbach 1975; Marbet et al. 1987; Mezey et al. 1988; Tuyns and Pequignot 1984). However, many individuals who consume this amount of alcohol do not develop liver disease. Less than one-half of heavy drinkers develop alcoholic hepatitis or liver fibrosis (Lelbach 1975), which suggests that other factors, perhaps hereditary, environmental, or both, interact with alcohol to affect the natural history of liver disease. That other factors contribute to the pathogenesis of liver disease in alcoholics is emphasized in a study by Marbet et al. (1987), who show that although a substantial amount of alcohol is required to induce liver injury, alcohol dose alone is not a good predictor of the severity of liver injury.

The mechanisms leading from chronic alcohol consumption to serious liver disease are not completely clear. The sections below review numerous possibilities supported by current investigation. Following this

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[1] For a definition of *fibrosis* and other terms, see the glossaries in the major sections of this chapter.

[2] Six hundred kilograms of alcohol represents approximately 72 ounces of beer, 1 liter of wine, or 8 ounces of distilled spirits consumed daily for 20 years.

Glossary

Adduct—A molecule formed by one molecule attached to another; for example, by attachment of acetaldehyde to a protein.

Adenocarcinoma—A form of glandular cancer; a malignancy of epithelial cells forming a glandular or gland-like structure.

Adhesion—The property of remaining close or attaching to a cell or tissue.

Alcohol dehydrogenase (ADH)—The primary enzyme responsible for the breakdown of alcohol. ADH catalyzes the formation of acetaldehyde from alcohol.

Aldehyde dehydrogenase (ALDH)—An enzyme that breaks down acetaldehyde formed from alcohol by *alcohol dehydrogenase.*

Aldehyde oxidase—An enzyme that breaks down aldehydes to acids and generates *superoxide anion* as a byproduct.

Allele—One of two or more different forms of the same gene.

Antioxidant—A substance that inhibits chemical *oxidation.*

Arachidonic acid—An essential *fatty acid* occurring in animal fats and also synthesized in the body from dietary linoleic acid, a constituent of many vegetable oils. *Leukotrienes, prostaglandins,* and *thromboxanes* are formed from arachidonic acid.

Chelator—A substance that combines with a metal.

Chemoattractant—A chemical that attracts migratory cells such as *neutrophils.*

Cirrhosis—A disease characterized by *fibrosis,* nodules, and loss of the normal structure of the liver accompanied by decline in liver function.

Collagen—The major protein constituent of connective tissue.

Cytochrome—A protein that serves as an electron carrier in the breakdown and release of energy from nutrient molecules by reaction with oxygen.

Cytochrome p450 2E1—A *microsomal enzyme* that plays an important role in alcohol metabolism but also produces *free radicals.*

Cytokine—A substance that regulates cellular interactions and cellular functions. Cytokines are produced by a variety of cell types throughout the body.

Cytosol—The fluid substance within a cell.

Cytotoxic—Toxic to cells.

Endothelium—The layer of cells that lines the blood vessels.

Endotoxin—A component of bacterial outer cell membranes that acts as a potent stimulus for many inflammatory cells.

Epithelium—The covering or lining tissue of the body.

Fatty acid—Long-chain organic acid found in lipids (fats and oils). Unsaturated fatty acids have no double bonds in their structure; polyunsaturated fatty acids have two or more double bonds.

Fibrosis—The formation of fibrous tissue in the liver.

Free radicals—A group of short-lived, electrically charged, highly reactive atoms incapable of existing in a free state for a prolonged period.

Glutathione—A sulfur-containing compound found in high concentrations in liver *cytosol* and *mitochondria.* Glutathione is an *antioxidant.*

Hyperplastic—Pertaining to hyperplasia, an abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue.

Hypoxia—Reduction of oxygen supply to tissue below physiologic levels despite adequate blood supply.

In vitro—Observable in a test tube or other artificial environment.

In vivo—Within the living body.

Leukotriene—A product of *arachidonic acid* metabolism that may play a role in allergic reactions and may be a mediator of inflammation.

Liver lobules—The functional units of the liver. Each lobule is composed of plates of hepatic cells arranged, spokelike, around a central vein. Plates of hepatic cells are separated by blood vessels feeding from branches of the hepatic artery to the central vein and vessels that accept bile produced by hepatic cells and transport it to bile ducts.

review is a discussion of hereditary and environmental factors that may affect the susceptibility of certain people to alcoholic liver disease or that may modify the progression of liver disease.

Putative Mechanisms of Alcoholic Liver Injury

Free Radical Formation

Alcohol metabolism by hepatocytes requires oxygen. As alcohol and oxygen are consumed, the body often produces *free radicals,* including hydroxyl and 1-hydroxyethyl radicals and *superoxide anions* (Kukielka et al. 1994; Rashba-Step et al. 1993; Reinke et al. 1991, 1994). These compounds are highly reactive and can interact with proteins, lipids, and deoxyribonucleic acid (DNA), thereby causing damage or death to liver cells (Fromenty et al. 1995; Nordmann et al. 1992). When free radicals attack unsaturated lipids in cell membranes, the result is a deleterious chain reaction of lipid radical formation known as lipid *peroxidation* (Carini et al. 1992). This reaction can be monitored in liver cells and tissues by a method that measures its chemical by-products. Several investigators have used this method to demonstrate that chronic alcohol consumption induces hepatic lipid peroxidation in rats and that the degree of lipid peroxidation correlates positively with liver injury (Kamimura et al. 1992; Nanji et al. 1994*g*; Teare et al. 1994). *Cytochrome P450 2E1* (CYP2E1), a *microsomal enzyme* that is instrumental in alcohol metabolism but that also produces free radicals, is associated with both lipid peroxidation and liver damage (Castillo et al. 1992; Nanji et al. 1994*g,h*; Takahashi et al. 1992). The central role of CYP2E1 in the rat model of alcoholic liver injury has been demonstrated by

Liver sinusoids—Small, irregular blood vessels found in the liver.

Macrophage—A *phagocyte* found in tissues throughout the body. Macrophages have many other functions, including the production of substances that contribute to inflammation.

Messenger ribonucleic acid (mRNA)—A nucleic acid copy of genetic information that encodes proteins and participates in protein synthesis.

Metaplasia—A change in type of cells in a tissue to another type of cells that are not normal for that tissue.

Microsomal enzymes—Detoxifying enzymes associated with *microsomes*.

Microsomes—Fragments of the endoplasmic reticulum, an intracellular *organelle* that functions to transport materials through cells.

Mitochondria—Intracellular *organelles* that consume oxygen and generate high-energy metabolites such as adenosine triphosphate (ATP), a molecule used by cells to transfer energy from an energy-yielding to an energy-requiring event.

Neutrophil—A white blood cell that has phagocytic and degradative activities similar to those of *macrophages*.

Nitrosamine—Any of various organic compounds characterized by the chemical group NNO, some of which are carcinogens.

Organelle—Membrane-surrounded structures found within cells that contain enzymes and other components for performing specialized cell functions.

Oxidation—A type of chemical reaction involving the loss of electrons. See also *peroxidation*.

Oxidative stress—An imbalance between increased production of *free radicals* and decreased availability of *antioxidants*.

Parenchyma—A general term designating the functional elements of an organ.

Permeability—The property or state of being permeable; that is, allowing passage of a substance.

Peroxidation—Enzymatic *oxidation* of organic *substrates*, such as lipids, in the presence of hydrogen peroxide.

Phagocyte—A white blood cell capable of ingesting foreign particles and microorganisms.

Phenotype—The observable characteristics of an organism; the product of genetic makeup.

Phosphatidylcholine—A type of phosphate-containing lipid that is a major component of cell membranes.

Polymorphism—The occurrence of two or more different forms of the same genetic trait in a population.

Prostaglandins—A class of biologically active compounds that affect many physiologic activities, including blood pressure, muscle contraction, and body temperature.

Proteinase—One of a group of enzymes that break down proteins.

Squamous—*Epithelium* composed of flattened, plate-like cells.

Stellate cell—A star-shaped fibroblastic cell derived from an Ito cell, a fat-storing cell in the liver. Stellate cells have lost the high levels of vitamin A associated with Ito cells and have gained an ability to contract in response to endothelin, a *vasoconstrictor*.

Substrate—The specific compound acted upon by an enzyme.

Superoxide anion—A *free radical* that is an oxygen atom with an extra electron.

Synergistic—Describing the property of one agent to enhance the effect of another agent.

Thromboxanes—A group of compounds that are derived from *arachidonic acid* and are biochemically related to *prostaglandins*.

Transcription—The enzymatic process of protein synthesis whereby genetic information encoded in one strand of DNA is used to specify a complementary sequence of nucleic acids in a *messenger RNA* (mRNA) chain.

Vasoconstrictor—A substance that causes constriction of blood vessels.

coadministration of alcohol with agents that inhibit CYP2E1; these studies showed that inhibition of CYP2E1 reduces alcohol-induced lipid peroxidation and limits liver damage (Morimoto et al. 1993, 1995).

Induction of alcoholic liver injury in rats requires administration of alcohol with a diet rich in polyunsaturated fat (Tsukamoto et al. 1990). The fat has two important effects: It markedly enhances CYP2E1 activity (which also is increased by alcohol alone), and it alters the membrane composition of hepatic *microsomes*, thereby favoring "peroxidizability" (Nanji et al. 1994*d,h* [p. 1281]). These two alterations serve to amplify alcohol-induced free radical production and lipid peroxidation. Alcohol-induced lipid peroxidation is likely to be less severe in human alcoholics than in experimental animals; nevertheless, when it occurs it may contribute to alcoholic liver injury. Indeed, some evidence suggests that alcoholic liver disease occurs more frequently in populations that consume a diet high in polyunsaturated fat (Nanji and French 1986).

Inflammatory cells that reside in the liver also may produce free radicals in response to alcohol. For example, Kupffer cells (liver *macrophages*) produce superoxide anion in response to either acute or chronic alcohol exposure (Bautista et al. 1992; Bautista and Spitzer 1992). Chronic alcohol consumption also causes circulating white blood cells known as *neutrophils* to migrate to the liver. If activated by an inflammatory substance such as *endotoxin* (a component of bacterial outer cell membranes), neutrophils may contribute to liver pathology by releasing large amounts of superoxide (Bautista et al. 1992).

Impaired Antioxidant Defense

Liver cells are normally equipped with an array of *antioxidants* that can neutralize free radicals. However, chronic alcohol consumption diminishes the levels of these antioxidants, thereby creating *oxidative stress*, a condition that renders liver cells more susceptible to injury induced by free radicals.

Glutathione, one example of an antioxidant affected by alcohol, is a sulfur-containing compound normally present at high concentrations in liver *cytosol* and mitochondria. *Mitochondrial* glutathione levels are maintained by a transport process that pumps the compound from the cytosol. Alcohol preferentially reduces hepatic mitochondrial glutathione by interfering with the transport process (Fernandez-Checa et al. 1991). This depletion significantly impairs mitochondrial function (Garcia-Ruiz et al. 1994) and may cause liver cells to die, but depletion can be prevented in the livers of alcohol-fed animals by administration of S-adenosylmethionine (SAM) (Garcia-Ruiz et al. 1995). SAM is a glutathione precursor; however, its beneficial effect does not seem to result from conversion to glutathione. Instead, SAM may modify the mitochondrial membrane, thus preventing the transport defect and maintaining glutathione levels in the normal range (Garcia-Ruiz et al. 1995). This mechanism may explain the effects of SAM in attenuating liver injury in a baboon model of alcoholic liver disease (Lieber et al. 1990*a*).

> *The antioxidant vitamins A and E also are normally present in the liver, but their levels are reduced with chronic alcohol consumption.*

The antioxidant vitamins A and E also are normally present in the liver, but their levels are reduced with chronic alcohol consumption (Hagen et al. 1989; Leo et al. 1993). In rats, depletion of vitamin E enhances alcohol-induced lipid peroxidation and exacerbates liver injury (Kawase et al. 1989; Sadrzadeh and Nanji 1994). Despite these known effects, vitamin E has shown no substantial benefit in preventing or reversing alcoholic liver injury in experimental animals (Sadrzadeh et al. 1995), perhaps because it is a fat-soluble vitamin, which limits its absorption. Similarly, studies of vitamin A supplementation in animals have yielded somewhat disappointing results, in part because vitamin A has an inherent liver toxicity that restricts its therapeutic dose range (Ahmed et al. 1994; Leo et al. 1992). However, given the potential importance of antioxidants for reducing liver injury, antioxidant therapy will likely continue as an active area of study (see later discussion).

Hypoxia

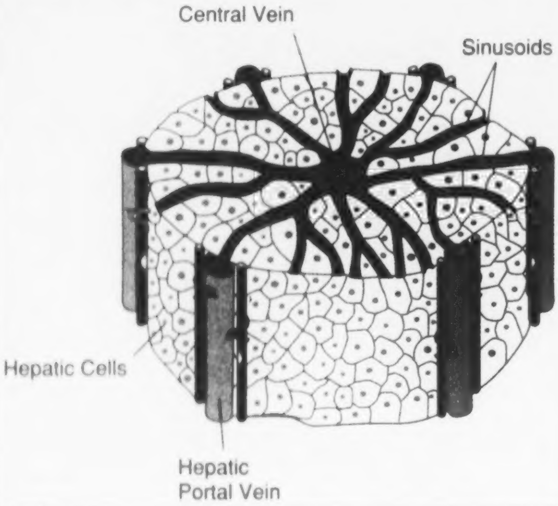
Blood enters the liver via the portal vein and traverses long channels called sinusoids before exiting via the central vein (figure 1). Because liver cells continuously extract oxygen from sinusoidal blood, the blood nearest the central vein contains less oxygen than that in the portal vein. Under normal circumstances, the amount of oxygen delivered to liver cells in the central vein region (the pericentral zone) is sufficient to support cellular metabolism; however, chronic alcohol ingestion increases oxygen consumption by liver cells (Israel et al. 1975, 1977). This increased demand for oxygen may not be met by the relatively oxygen-poor pericentral blood and may lead to *hypoxia* (oxygen deficiency) (Ji et al. 1982). Recent studies suggest that alcohol-induced pericentral hypoxia is driven by Kupffer cells. When Kupffer cells are selectively destroyed or their activation is prevented, hepatic oxygen tension returns to baseline levels, thereby halting alcoholic liver injury (Adachi et al. 1994, 1995). The mechanisms by which Kupffer cells cause these changes are unknown but may involve secretion of *vasoconstrictors*, which are compounds that constrict the sinusoids and reduce blood flow (Adachi et al. 1994, 1995).

Endothelial cells in *liver sinusoids* may contribute to alcohol-induced liver hypoxia by secreting endothelin, which is a potent vasoconstrictor that reduces blood flow by narrowing blood vessels. Acute alcohol infusion in the liver provokes endothelin production; the result may be profound hepatic vasoconstriction (Oshita et al. 1993). In addition, alcohol ingestion increases plasma levels of endothelin, presumably by increasing hepatic production (Nanji et al. 1994*b*). However, the role of endothelin in alcoholic liver injury remains to be fully characterized.

Eicosanoid Effects

Eicosanoids are metabolites of *arachidonic acid* that exhibit a wide range of biological activity. They comprise several classes of compounds, including *prostaglandins*, *thromboxanes*, and *leukotrienes*. Prostaglandins (especially prostaglandin E_2) are known for their protective effects on liver cells. In contrast, thromboxanes (such as thromboxane B_2) cause vasoconstriction and can be directly toxic to hepatocytes (Horton and Wood 1991). Leukotrienes may cause liver injury by attracting and activating neutrophils. Chronic alcohol consumption has been shown to reduce production of protective eicosanoids by liver cells (Nanji 1993; Nanji et al. 1994*c*) and enhances

Figure 1. Diagram of a liver lobule.



synthesis of thromboxane B$_2$; furthermore, inhibition of thromboxane synthesis can help prevent alcoholic liver injury in experimental animals (Nanji et al. 1994*f*).

Acetaldehyde Effects

Acetaldehyde, the first oxidative metabolite of alcohol, is a highly reactive compound that may promote hepatic injury and fibrosis. Acetaldehyde normally is metabolized rapidly to acetate, but acetaldehyde accumulates at higher levels in alcoholics (Baraona et al. 1987). If its concentrations become high enough, acetaldehyde can become a *substrate* for *aldehyde oxidase* and other enzymes that produce free radicals as byproducts of this reaction (Kato et al. 1990; Shaw and Jayatilleke 1990, 1992; Tsukamoto et al. 1995). Acetaldehyde also can react with specific amino acid residues on cellular proteins to form acetaldehyde-protein *adducts*. These adducts can be demonstrated in the livers of human alcoholics (Holstege et al. 1994; Niemela et al. 1991) and alcohol-fed animals (Lin et al. 1993*a*). In most instances, the adducts localize preferentially to the pericentral zone, where liver injury is often greatest. Acetaldehyde-protein adducts also may stimulate liver cells to produce *collagen*, which may result in fibrosis and, ultimately, cirrhosis (Bedossa et al. 1994; Casini et al. 1993).

In addition, acetaldehyde may form adducts with the proteins that form the cellular microstructure (Smith et al. 1992*a*; Tuma et al. 1991). These proteins provide mechanical support and are essential to a variety of intracellular activities. Reaction with acetaldehyde can impair assembly of this support system, which may in turn disturb important transport processes in liver cells. These processes include uptake of extracellular compounds (Casey et al. 1993; Rees et al. 1993) and secretion of proteins (Volentine et al. 1987). Acetaldehyde-induced impairment of protein secretion has been implicated in the swelling ("ballooning") of liver cells observed in alcoholic liver disease (Tuma and Sorrell 1988).

Cytokine Effects

Cytokines are a diverse group of substances with inflammatory, fibrogenic, and growth-promoting properties. Many are associated with alcoholic liver disease and are under active investigation as mediators of liver injury. Patients with alcohol-induced liver inflammation (alcoholic hepatitis) frequently have high circulating levels of the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-alpha) (Bird et al. 1990; Hill et al. 1992, 1993; Khoruts et al. 1991; Ohlinger et al. 1993; Sheron et al. 1993; Tilg et al. 1992). IL-8 and TNF-alpha, in particular, correlate negatively with prognosis of liver disease (Felver et al. 1990; Hill et al. 1992, 1993; Sheron et al. 1993). Transforming growth factor-beta (TGF-beta), another cytokine found in the livers of alcoholics, plays a critical role in hepatic fibrosis.

Because cytokines exert their greatest biological activity locally, investigators have examined cytokines produced in the liver in response to alcohol. Of particular interest are those whose levels correlate temporally with both the onset and the progress of liver injury. TNF-alpha satisfies both of these criteria. In rats, hepatic TNF-alpha *messenger ribonucleic acid* (mRNA) rises after 1 month of alcohol feeding, which correlates with the onset of liver cell necrosis and inflammation (Nanji et al. 1994*i*); this TNF-alpha appears to be derived primarily from Kupffer cells (Hansen et al. 1994). TNF-alpha may have direct *cytotoxic* effects on hepatocytes (Shinagawa et al. 1991) or may cause indirect harm by stimulating hepatocytes to produce IL-8. This latter cytokine attracts neutrophils that may, in turn, contribute to inflammation (Thornton et al. 1990, 1991). TNF-alpha also promotes *adhesion* of white blood cells to the sinusoidal *endothelium* stimulating the release of superoxide and toxic *proteinases*, which is perhaps the most serious consequence of hepatic TNF-alpha production (Gorczynski et al. 1994; Hoffmann et al. 1993; Komatsu et al. 1994; Ohira et al. 1994).

IL-8, a potent *chemoattractant* and stimulator of neutrophils (Baggiolini et al. 1994), is found in the livers of patients with alcoholic hepatitis (Sheron et al. 1993). IL-8 in the liver is thought to play a role in the migration of neutrophils into hepatic *parenchyma*. In addition, chronic alcohol exposure stimulates IL-8 production in rat hepatocytes and Kupffer cells (Bautista 1995; Shiratori et al. 1993). The mechanisms by which alcohol stimulates IL-8 production are unknown, although hepatocyte IL-8 gene expression is inducible by oxidant stress (DeForge et al. 1993) and by TNF-alpha (Thornton et al. 1991). IL-8 is not the only alcohol-inducible neutrophil chemoattractant produced in the liver; others include 19-hydroperoxy, 20-hydroxy-arachidic acid (Roll et al. 1992) and 4-hydroxynonenal (Esterbauer et al. 1991). The relative contribution of these various substances to alcohol-induced hepatic inflammation is an area of active study.

Role of Kupffer Cells and Endotoxin

Kupffer cells are emerging as important contributors to alcoholic liver injury. In addition to their role in free radical-induced and hypoxic liver damage, these cells produce cytokines (including TNF-alpha and TGF-beta) in response to alcohol. TNF-alpha and TGF-beta may cause direct tissue damage, enhance alcohol-induced hepatic inflammation, or both (Hansen et al. 1994; Matsuoka and Tsukamoto 1990). Kupffer cells may also influence the rate of alcohol metabolism by liver cells (Bradford et al. 1993). Experiments in alcohol-fed rats whose Kupffer cells were selectively eliminated have shown that these rats consumed as much alcohol as their corresponding controls but, unlike their corresponding controls, exhibited no signs of alcohol-induced liver injury (Adachi et al. 1994). These findings demonstrate a central role for Kupffer cells in alcoholic liver injury.

Although the mechanisms whereby alcohol activates Kupffer cells are unknown, several studies point to endotoxin as an important cofactor. As mentioned earlier, endotoxin is a component of the bacterial cell membrane that acts as a potent stimulus of many inflammatory cells. Chronic alcohol ingestion is thought to allow endotoxin, which is derived presumably from bacteria that normally reside in the gut, to enter the circulation by increasing intestinal *permeability*. Several studies have shown that endotoxin interacts with alcohol to stimulate Kupffer cells. For example, when Kupffer cells from alcohol-fed animals are challenged with endotoxin, the cells produce more TNF-alpha and release more superoxide than Kupffer cells from normal and alcohol-fed control animals. Circulating levels of endotoxin can be reduced in alcohol-fed rats by administration of antibiotics (Adachi et al. 1995) or lactobacillus (a bacterium that displaces bacteria normally found in the intestines) (Nanji et al. 1994*a*). Both approaches substantially reduce alcohol-induced liver injury.

Immune Responses to Altered Hepatocellular Proteins

Chronic alcohol ingestion may lead to autoimmune liver injury. One autoimmune process involves antibodies that bind to liver cells and target them for destruction by inflammatory cells. (A more extensive discussion of the cells and mechanisms of autoimmune liver injury is found in a later section of this chapter.) To be recognized as "foreign" by the immune system, liver cells first must be altered. Acetaldehyde and hydroxyethyl radicals can accomplish this task by forming adducts with proteins on the liver cell surface; indeed, antibodies directed against such modified proteins are detectable in the blood of alcoholic patients (Clot et al. 1995; Hoerner et al. 1988; Niemela et al. 1987) and may even serve as markers of alcohol abuse in some people (Lin et al. 1993*b*). Adducts of liver cell surface proteins, such as liver membrane antigen and CYP2E1, are possible targets of immune-mediated alcoholic liver injury (Behrens et al. 1988; Takase et al. 1993; Wu and Cederbaum 1992).

Protein adducts implicated as autoimmune targets also include intracellular rather than cell surface proteins. Some, such as collagen, are deposited in extracellular spaces (Behrens et al. 1990); others are found inside liver cells or in the circulation (Donohue et al. 1983; Kurki et al. 1984; Stevens et al. 1981; Tuma et al. 1987). Whether antibodies directed against these proteins induce liver injury is uncertain.

Mechanisms of Alcoholic Liver Fibrosis

Among the many adverse effects of alcohol on the liver, fibrosis (scarring) is of major importance because it leads to irreversible cirrhosis. Chronic alcohol consumption induces liver fibrosis by stimulating the fat-storing cells of the liver, known as Ito cells, to differentiate into *stellate cells*, which produce collagen. The precise stimuli that initiate and regulate this process *in vivo* are unknown. However, other compounds with known roles in alcoholic liver injury may contribute to fibrosis through effects on stellate cells. Acetaldehyde-protein adducts, for example, can enhance collagen synthesis by stellate cells *in vitro* (Bedossa et al. 1994; Casini et al.

1993; Moshage et al. 1990) by stimulating *transcription* of the collagen gene (Casini et al. 1991; Pares et al. 1994). Products of lipid peroxidation also increase collagen synthesis (Maher et al. 1994; Parola et al. 1993; Tsukamoto 1993). A third potential contributor is TGF-beta, which is a potent stimulator of collagen synthesis by stellate cells (Armendariz-Borunda et al. 1992). Chronic alcohol feeding induces TGF-beta production by Kupffer cells, and stellate cells from alcohol-fed rats have an enhanced sensitivity to the fibrogenic effects of TGF-beta (Matsuoka and Tsukamoto 1990). Recent studies have shown that TGF-beta is also produced by stellate cells in the liver of alcoholics (Castilla et al. 1991); this production of TGF-beta may contribute to liver damage by creating a self-perpetuating stimulus to ongoing fibrosis.

In addition to TGF-beta, Kupffer cells may produce other compounds that influence development of alcoholic liver fibrosis. Matsuoka et al. (1990) have shown that Kupffer cells from alcohol-fed rats secrete a factor that stimulates growth of stellate cells. Thus, Kupffer cells may indirectly enhance fibrosis by increasing the number of stellate cells (Matsuoka et al. 1990).

> *Women seem to be more susceptible to serious alcoholic liver injury; they develop cirrhosis at a lower cumulative dose of alcohol than men do.*

Hereditary and Environmental Cofactors Implicated in Alcoholic Liver Injury

Hereditary Variations in Alcohol Metabolism

In an effort to explain why only a small proportion of alcoholics develop serious liver disease, investigators have suggested that hereditary variations in enzymes that metabolize alcohol may contribute to risk. *Polymorphisms* (or genetic variants) in *alcohol dehydrogenase* (ADH), CYP2E1, and *aldehyde dehydrogenase* (ALDH) are under study. Numerous polymorphisms exist for ADH; these result in large differences in the rates of alcohol metabolism among different ethnic groups (Hanna 1978). Despite these findings, no single ADH *allele* has been firmly linked to the development of alcoholic liver injury (Chao et al. 1994; Day et al. 1991; Poupon et al. 1992).

A polymorphism in CYP2E1 has been identified in a region of the gene that controls transcription (Hayashi et al. 1991). People who have this rare allele, called *c2*, have higher baseline CYP2E1 activity than those who do not (Tsutsumi et al. 1994). This higher activity may contribute to liver damage through increased generation of toxic free radical byproducts of alcohol metabolism. A study of 284 Japanese subjects has found *c2* to be more than twice as common in patients with alcoholic liver disease than in healthy control subjects or patients with liver disease unrelated to alcoholism (Tsutsumi et al. 1994). The same study found that the *c2* allele could not be identified in alcoholics without liver disease, which underscores the potential importance of *c2* as a risk factor for alcoholic liver disease among the Japanese.

ALDH polymorphisms also have been implicated in the development of alcoholic liver injury. An allele known as $ALDH2^2$ is present in about 50 percent of the Chinese and Japanese; it encodes an enzyme that is completely inactive toward acetaldehyde. People with two copies of this allele ($ALDH2^2$ homozygotes) generally have an aversion to alcohol because they rapidly develop acetaldehyde toxicity (flushing and nausea) after drinking. However, some people with only one copy of the gene ($ALDH2^2$ heterozygotes) are habitual drinkers and develop liver injury with higher frequency and at a lower cumulative dose than people with a normal ALDH *phenotype* (Enomoto et al. 1991).

Gender

Women seem to be more susceptible to serious alcoholic liver injury; they develop cirrhosis at a lower cumulative dose of alcohol than men do (Marbet et al. 1987; Mezey et al. 1988; Tuyns and Pequignot 1984). In addition, compared with men, women who have alcoholic liver injury remain at substantially higher risk of disease progression even with abstinence (Galambos 1972; Pares et al. 1986).

Two hypotheses have been proposed to explain gender-specific differences in the risk of alcoholic liver disease. The first implicates gastric ADH as a causative factor. Although ADH is present in high levels in the liver, it also is found in the stomach and intestine (Pestalozzi et al. 1983), and metabolism of alcohol by gastric ADH limits the amount of ingested alcohol that ultimately reaches the liver. Some studies have shown that women have lower levels of gastric ADH activity than men (Frezza et al. 1990; Seitz et al. 1992), which suggests that dose for dose, women may deliver more concentrated levels of alcohol to the liver and therefore may exhibit earlier signs of liver toxicity. However, other investigators have found no such gender differences in gastric ADH activity (Thuluvath et al. 1994), and some researchers question whether the stomach plays a significant role in first-pass metabolism of alcohol (Levitt and Levitt 1994).

The second hypothesis holds that accelerated alcoholic liver injury in women may be related to gender differences in the metabolism of *fatty acids*. Using animal models to study liver injury, researchers have consistently shown an important role for fat in the disease process (Lieber and DeCarli 1970). Chronic alcohol consumption inhibits beta-oxidation of fatty acids by hepatic mitochondria (Lieber et al. 1965). Disruption of this process may lead to an accumulation of nonmetabolized fatty acids in liver cells and ultimately to liver cell injury. This problem may be circumvented by diversion of fatty acids to alternate, compensatory metabolic routes. Recent studies have shown that one compensatory pathway is efficiently stimulated in alcohol-fed male rats but not in alcohol-fed female rats (Ma et al. 1993). In addition, the binding capacity of fatty acid binding proteins, which assist in fatty acid metabolism, also is reduced in alcohol-fed female rats relative to alcohol-fed male rats (Shevchuk et al. 1991); this finding provides additional support for fatty acid toxicity in causing liver injury in alcoholic women.

Diet and Nutrition

Studies in baboons indicate that alcohol induces liver injury despite adequate protein-calorie and vitamin nutrition (Lieber et al. 1965); these studies indicate that alcohol alone has some inherent toxicity regardless of nutritional status. In humans, however, alcoholic liver injury is strongly associated with nutrition (Mendenhall et al. 1986). Numerous dietary factors may facilitate or precipitate alcoholic liver injury. For example, depletion of antioxidant vitamins and glutathione can enhance oxidative stress in the liver, as discussed earlier. A diet high in polyunsaturated fat increases levels of CYP2E1, which may permit accumulation of substrates for alcohol-induced lipid peroxidation in the liver and thereby contribute to oxidative stress (Nanji et al. 1994*a*,*b*). Chronic alcohol ingestion promotes absorption of iron from the intestine and increases hepatic iron stores. In view of its role in free radical production, increased hepatic iron might be expected to contribute to oxidative alcoholic liver injury (Mendenhall et al. 1986; Shaw and Jayatilleke 1992; Tsukamoto et al. 1995).

Coexistent Viral Hepatitis

Infection with the hepatitis C virus (HCV) acts at least additively, if not *synergistically*, with alcohol to increase risk of liver injury (Corrao et al. 1991; Parrish et al. 1991). Roughly 18 to 25 percent of alcoholics exhibit signs of HCV infection. In alcoholics with liver injury, this proportion can increase to more than 40 percent (Nalpas et al. 1991; Pares et al. 1990). Although this percentage is lower in some studies, there is general agreement that alcoholics infected with HCV develop liver injury at a younger age and at a lower cumulative dose of alcohol than noninfected alcoholics do (Caldwell et al. 1993; Mendenhall et al. 1991). These findings may be related to observed effects of alcohol in enhancing HCV replication, in depressing the host immune response to the virus, or both (Oshita et al. 1994; Sawada et al. 1993).

Hepatitis B virus infection also increases the incidence of chronic liver injury in alcoholics. Epidemiologic data suggest that this virus poses an additive, rather than a synergistic, risk of liver injury in combination with alcohol (Corrao et al. 1991; Mendenhall et al. 1991).

Coffee Drinking and Cigarette Smoking

Alcoholics who smoke more than one pack of cigarettes per day have three times the risk of cirrhosis than those who do not smoke. By contrast, alcoholics who consume four or more cups of coffee daily have a fivefold lower incidence of cirrhosis than those who do not drink coffee. The reason for the synergistic effect of smoking and the protective effect of coffee is uncertain; the effect of coffee may be unrelated to caffeine, as drinking tea does not appear to afford the same benefit (Klatsky and Armstrong 1992).

Treatment of Alcoholic Liver Disease

Some studies have shown that corticosteroids are beneficial in treating severe alcoholic hepatitis (Carithers et al. 1989; Ramond et al. 1992). Aggressive nutritional support also is recommended, and in some, but not all, instances it improves patient survival (Mendenhall et al. 1991). In view of their potential importance in preventing or reducing oxidant stress, antioxidants also may be therapeutic. To this end, researchers are actively investigating vitamins A and E and SAM as therapeutic agents (Butcher et al. 1993). The emergence of endotoxin as a possible contributor in alcoholic liver disease may lead to antibiotic therapy or to the development of inhibitors targeted at reducing Kupffer cell and neutrophil activities.

One group of investigators has characterized polyunsaturated soybean lecithin as a possible therapeutic agent. Polyunsaturated soybean lecithin dramatically reduced the incidence of cirrhosis in alcohol-fed baboons (Lieber et al. 1990*b*, 1994). The active compounds in this mixture are various forms of *phosphatidylcholine*, which are thought to exert beneficial effects by promoting degradation of hepatic collagen (Li et al. 1992).

Effects of Alcohol on the Esophagus, Stomach, and Intestines

Alcohol has been implicated as a cause of chronic esophageal inflammation that sometimes leads to esophageal cancer. Inflammation occurs in part because alcohol inhibits contraction of the smooth muscle in the lower esophagus (Keshavarzian et al. 1994). Poor contraction at the junction of the esophagus and stomach can precipitate reflux of gastric acid that, in turn, may precipitate conditions that range in severity from heartburn to severe esophagitis (inflammation of the esophagus). Prolonged reflux may lead to a permanent alteration, or *metaplasia*, of the esophageal lining called Barrett's esophagus, and patients with this condition have a high risk of progression to esophageal *adenocarcinoma* (Gray et al. 1993).

People who consume more than 21 drinks per week have almost a tenfold higher risk of esophageal cancer than those who drink fewer than 7 drinks per week.

People who consume more than 21 drinks per week have almost a tenfold higher risk of esophageal cancer than those who drink fewer than 7 drinks per week (Vaughan et al. 1995). These esophageal cancers include adenocarcinomas as well as squamous cell carcinomas, which are cancers that arise in the normal (*squamous*) esophageal lining. Both types of carcinomas may be provoked by local actions of alcohol metabolites or alcohol-metabolizing enzymes on esophageal cells. ADH is present in the esophageal mucosa (Yin et al. 1993). The acetaldehyde produced by the breakdown of alcohol may alter normal DNA repair mechanisms in esophageal cells, thus leading to gene alterations that may contribute to tumor formation (Wilson et al. 1994). Alcohol consumption also increases levels of CYP2E1 in the esophageal mucosa, which can activate other dietary carcinogens (such as *nitrosamines*) (Shimizu et al. 1990). Of note, smoking and drinking interact to enhance the risk of esophageal cancer even further (Blot 1994).

Alcohol consumption is not associated with a risk of stomach cancer (Franceschi and La Vecchia 1994), but it may cause gastritis (inflammation of the stomach). With the recent recognition that gastritis and ulcer disease in nonalcoholics often are caused by the bacterium *Helicobacter pylori* (*H. pylori*), intense interest has developed in examining the role of *H. pylori* in alcoholic gastritis. Heavy drinkers have a higher incidence of gastritis and of *H. pylori* infection than do light drinkers; this finding suggests that alcoholic gastritis may be attributed to *H. pylori* infection rather than to alcohol per se (Paunio et al. 1994). Consistent with this notion is research showing that alcoholic gastritis is not readily cured by abstinence but is improved by treatment with antibiotics (Uppal et al. 1991). Davies et al. (1994) recently have shown that *H. pylori*, but not alcohol, induces production of oxygen radicals in the stomach.

Because *H. pylori* possesses ADH (Kaihovaara et al. 1994), it has the potential to enhance gastric alcohol metabolism. However, patients with *H. pylori* infection have lower gastric ADH activity than noninfected control subjects do (Salmela et al. 1994; Thuluvath et al. 1994). Thus, any potential contribution of the organism to alcohol metabolism in vivo appears to be offset by its damage to ADH-producing cells in the stomach.

Some studies point to alcohol as a risk factor for colorectal cancer, although there is debate over this issue (Giovannucci and Willet 1994). Nutritional factors likely play a role in alcohol-related colon cancer in humans; this hypothesis is supported by studies that show alcohol in combination with a diet low in methionine and folate (which are essential nutrients) measurably increase the risk for colon cancer (Giovannucci and Willet 1994; Giovanucci et al. 1995). Alcohol also induces the formation of benign (*hyperplastic*) polyps in the colon and rectum in humans (Kearney et al. 1995); this fact corresponds with observations in rats that alcohol feeding stimulates replacement of rectal cells (Seitz et al. 1990; Simanowski et al. 1986). Others have shown that colonic bacteria can metabolize alcohol to acetaldehyde (Jokelainen et al. 1994; Seitz et al. 1990); in the setting of increased intestinal cell growth, acetaldehyde may facilitate DNA mutations that lead to tumor formation.

Alcohol-Induced Pancreatic Injury

Alcohol abuse can lead to chronic pancreatic inflammation, atrophy, and fibrosis. Although only a small proportion of alcoholics develop pancreatic injury, specific risk factors that predispose people to pancreatic disease have been difficult to identify (Haber et al. 1995). The mechanisms leading to alcoholic pancreatitis also are poorly understood. Some animal models implicate free radicals as mediators of pancreatic injury. For example, when acetaldehyde is infused into the pancreas, to increase the activity of an enzyme that produces free radicals, an acute inflammation is induced. This inflammation can be inhibited by reducing agents, which neutralize free radicals, and iron *chelators*, which prevent iron from promoting the formation of free radicals (Nordback et al. 1995). In animal models of chronic alcohol exposure, lesions similar to those of human alcoholic pancreatitis can be induced when alcohol is administered with a diet high in polyunsaturated fat (Horne and Tsukamoto 1993). As with alcoholic liver disease, that polyunsaturated fat potentiates pancreatic injury implicates free radicals as contributors to this injury process. Antioxidant depletion may also be important. In models of acute pancreatitis unrelated to alcohol exposure, glutathione depletion has been observed. This depletion appears to facilitate activation of pancreatic enzymes within the organ, thus precipitating an "autodigestion" of pancreatic tissues (Luthen et al. 1995). Whether depletion of pancreatic glutathione is a factor in the pathogenesis of alcoholic pancreatitis remains to be determined (Luthen et al. 1994). However, local activation of pancreatic enzymes appears to play a key role in tissue injury in alcoholic pancreatitis (Foitzik et al. 1994).

Cardiovascular Effects of Alcohol

An association between excessive alcohol consumption and cardiac dysfunction has been recognized for more than a century, but the direct role of alcohol as opposed to accompanying nutritional deficiencies has come into focus only recently (Rubin and Thomas 1992). Some degree of subclinical depression of heart function is apparent in a large proportion of alcoholics (Davidson 1989; Rubin and Urbano-Marquez 1994). Heavy alcohol drinking (more than four drinks per day) has been associated with a variety of detrimental effects on the heart and *vascular* system (Davidson 1989); by contrast, moderate alcohol consumption (up to two drinks per day) may have some beneficial effects (Klatsky 1994). Considerable advances in elucidating the mechanisms behind these effects have formed the basis for a better understanding of the processes involved in cardiovascular disease induced by alcohol. This section reviews current knowledge about known targets of alcohol in the cardiovascular system and focuses on alcohol's effects on the heart itself and on circulatory function.

At the level of the heart muscle, long-term heavy consumption of alcohol can lead to alcoholic *cardiomyopathy*, which is characterized by loss of contractile function and enlargement of the heart. In addition, defects in the electrical conduction properties of the heart brought on by acute or chronic alcohol abuse can result in arrhythmias, or disturbances in the rhythm and synchronization of the heartbeat. At the level of the circulatory system, chronic alcohol intake is associated with *hypertension*; heavy drinking also increases the risk for cerebrovascular disorders, which diminish the blood supply in the brain and may lead to *stroke*. However, epidemiologic evidence suggests that moderate alcohol consumption may have a protective effect against *coronary artery disease* (CAD), a condition characterized by insufficient blood supply to the heart muscle.

The Heart

Cardiomyopathy

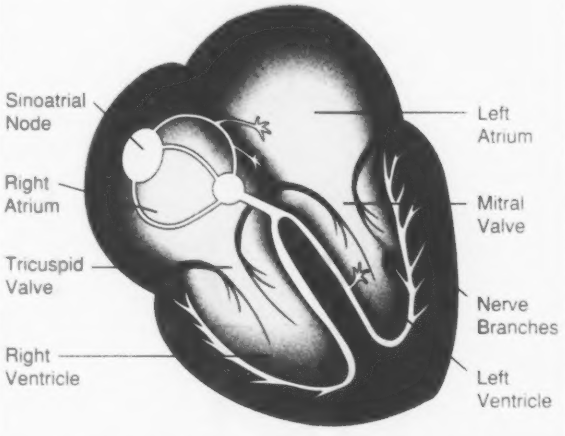
Any intrinsic degenerative disease of the heart muscle may be referred to as "cardiomyopathy." Alcoholic cardiomyopathy reflects low-output *congestive heart failure* with clinical symptoms and pathology that are indistinguishable from other forms of *dilated cardiomyopathy* (Regan 1990; Rubin and Doria 1990). This disease progresses from an asymptomatic stage in which the contractile function of the heart is compromised. These initial deficiencies are compensated by a variety of mechanisms, including dilation of the ventricles (the pumping chambers of the heart), an increase in the bulk of heart muscle (*cardiac hypertrophy*), and an increase in blood volume. Eventually, the compensatory mechanisms break down; as a result, the heart cannot pump enough blood to meet the body's normal requirements. In this phase, known as *cardiac decompensation*, patients experience shortness of breath and fatigue, and deficiencies in oxygenation are exacerbated by increased blood volume. Finally, heart failure may progress to a point at which *cardiac output* can no longer sustain life.

Chronic alcohol abuse is thought to be the underlying cause in an estimated 20 to 50 percent of all cases of dilated cardiomyopathy (McCall 1987; Regan 1990). Alcoholic cardiomyopathy usually develops over years (more than 10) of excessive drinking; clinical symptoms most often become evident between 30 and 60 years of age. The disease appears to be more common in men than in women, but this observation may simply reflect the greater prevalence of alcoholism in men (Rubin and Thomas 1992). Recent studies comparing the deleterious effects of alcohol on heart function in alcoholic women and men indicate that women are at least as sensitive as men to alcohol's cardiotoxic effects (Kupari and Koskinen 1992; Rubin and Urbano-Marquez 1994). Although nutritional deficiencies may exacerbate some cardiovascular effects of alcoholism, it is now clear that alcohol has direct toxic effects on heart muscle and that this is the primary cause of alcoholic cardiomyopathy (Davidson 1989; Estruch et al. 1993). One study found reduced ejection fractions (the proportion of blood ejected from the heart at each beat) in one-third of a group of well-nourished alcoholics (Urbano-Marquez et al. 1989). These investigators also found that the depression of cardiac contractile function and the observed increase in heart mass correlated with total lifetime consumption of alcohol; their finding indicates that there may be a dose-dependent component to alcohol's effect. Alcoholic cardiomyopathy may be reversible with abstinence if the disease is not too far advanced; that is, while it remains in a subclinical state. However, even with abstinence, patients with severe symptoms may progress to congestive heart failure and death (Regan 1990; Rubin and Doria 1990; Rubin and Urbano-Marquez 1994).

In recent years, considerable progress has been made in understanding how alcohol interferes with the mechanical function of the heart (reviewed in Piano and Schwertz 1994; Thomas et al. 1994). Effects of alcohol may be acute (changes that are dependent on the immediate presence of alcohol) or chronic (changes that develop over an extended period of regular alcohol consumption). Establishing experimental models that reproduce the low-output form of congestive cardiomyopathy seen in long-term alcoholics has been an elusive goal; however, changes occurring over relatively shorter times can be studied in animals fed alcohol as part of their diet. In addition, whereas overt responses of the heart to acute alcohol exposure reverse rapidly once alcohol is no longer present, repeated episodes of acute alcohol exposure can lead to cumulative damage and adaptation of the cardiovascular system that likely contribute to the development of alcoholic heart disease. Therefore, investigations of both acute and chronic actions of alcohol on heart biochemistry and physiology are important for defining the basis of alcohol-induced heart disease.

Figure 2. The heart's electrical system.

The heart's electrical system stimulates the contraction of the muscle cells of the four chambers, thereby causing blood to circulate through the chambers in a precise and sequential fashion. The stimulation begins in the sinoatrial node, proceeds through the atria, then moves through the ventricles.



Acute alcohol exposure causes a direct depression of the contractile function of heart muscle. This effect may be masked somewhat by an indirect stimulation of the heart resulting from an alcohol-induced elevation of *catecholamines*, such as adrenaline (Cheng et al. 1990). At one time, direct suppressive effects of alcohol were thought to result from alterations in energy metabolism of the heart, but recent evidence suggests alcohol also interferes with steps controlling contraction (Schulman et al. 1991).

Heart muscle contraction is triggered by electrical impulses that pass rapidly through the heart (figure 2). The impulses cause an increase in the concentration of calcium ions within the heart muscle cells; in turn, calcium ions activate the proteins responsible for contraction. Recent technical advances have allowed investigation of this excitation-contraction process at the cellular level. Such studies have shown that changes in the concentration of calcium ions responsible for muscle contraction are reduced in the presence of high levels of alcohol (Guarnieri and Lakatta 1990; Kojima et al.

Glossary

Action potential—The electrical changes produced when a membrane becomes polarized and ion movement occurs. These changes involve phases of *depolarization* and *repolarization.*

Adenosine triphosphate (ATP)—A molecule used by cells to transfer energy from an energy-yielding to an energy-requiring event.

Angina—Spasmodic, choking, or suffocating pain, usually denoting *angina pectoris.*

Angina pectoris—The acute pain that accompanies *ischemia* in the *myocardium.*

Antithrombotic—Preventing or interfering with the formation of a *thrombus.*

Apolipoprotein—A protein associated with *high-density lipoprotein* (HDL) or *low-density lipoprotein* (LDL).

Atherosclerosis—A condition in which deposition of materials, often fat droplets, in the walls of arteries leads to narrowing and hardening of the arteries.

Atrial fibrillation—Loss of coordinated contraction of either or both atria.

Atrium—One of the two upper chambers of the heart.

Baroreceptors—Sensory *neurons* that perceive increases in pressure within the chambers of the heart and major vessels to regulate heart rate and *vascular resistance.*

Cardiac decompensation—A condition in which the heart cannot pump enough blood to meet the body's normal requirements.

Cardiac hypertrophy—An increase in the bulk of heart muscle resulting in enlargement of the heart.

Cardiac output—The product of stroke volume, or the amount of blood pumped with each beat, and the heart rate. Cardiac output is used as a measure of how efficiently the heart is serving the body's needs.

Cardiomyopathy—A general term for primary noninflammatory disease of the *myocardium.* See also *dilated cardiomyopathy.*

Catecholamine—A compound having actions in the body that mimic actions of the sympathetic nervous system, which controls automatic processes such as heart rate.

Cerebrovascular disease—Disease affecting the blood vessels of the brain.

Congestive heart failure—Progressive inability of a diseased heart to pump sufficient blood to meet the demands of the body.

Coronary artery disease (CAD)—Disease resulting from restriction or interruption of blood supply to the heart muscle via the coronary arteries.

Depolarization—Process by which ion fluxes cause the electrical potential of the cell membrane to become more neutral. See *repolarization.*

Dilated cardiomyopathy—A form of *cardiomyopathy* in which one or more chambers of the heart are abnormally distended with blood.

Fatty acid ethyl ester—The product of the reaction of ethyl alcohol with a fatty acid.

High-density lipoprotein (HDL)—A type of protein found in the blood that consists of a lipid fraction and a protein fraction and that functions as a carrier of cholesterol. HDL has a higher proportion of protein to lipid than does *low-density lipoprotein* (LDL).

Hypertension—High blood pressure.

Hypomagnesemia—Nutritional deficiency of magnesium.

Inositol triphosphate—A molecule that participates in *intracellular signal transduction.*

Intracellular signal transduction—A series of intracellular reactions that occur after the interaction of a cell receptor with a stimulus, such as a hormone, resulting in functional changes within that cell.

Ischemia—Deficiency of blood in an organ or tissue, usually due to constriction or blockage of a blood vessel.

1993; Thomas et al. 1989). Targets for alcohol's action in producing this effect have been identified as specific channels in the cell membrane that control entry of calcium ions (Guarnieri and Lakatta 1990; Mongo and Vassort 1990) and the sarcoplasmic reticulum, an intracellular *organelle* that serves as a calcium storage unit (Danziger et al. 1991; Thomas et al. 1991). In addition, contractile proteins of the heart muscle appear to be less sensitive to calcium ion activation in the presence of alcohol, even at low concentrations (Danziger et al. 1991; Schulman et al. 1991).

Some morphological and biochemical changes observed in the hearts of human alcoholics can be mimicked in alcohol-fed animals. Of interest is the work of Capasso et al. (1991*a,b*; 1992), who observed a remodeling of the *myocardium* in the hearts of alcohol-fed rats. In these studies, alcohol exposure over a period of 8 months resulted in dilation of the left ventricular chamber and a decrease in the thickness of the muscle of the heart wall. Paralleling these morphological changes were marked depressions in cardiac performance and reductions in the contractility of isolated heart muscle. Prolonged alcohol consumption also reduces the ability of contractile proteins of the heart muscle to hydrolyze *adenosine triphosphate* (ATP), an energy-supplying metabolite that powers muscle contraction (Capasso et al. 1992; Reddy and Beesley 1990). Other studies in animal models have suggested that elevated catecholamine levels play a role in the hypertrophic response to alcohol; in these studies, alcohol-induced cardiac hypertrophy was prevented by specific catecholamine blockers (Adams and Hirst 1990; King and Hirst 1990).

Biochemical and *ultrastructural* studies have suggested that chronic alcohol consumption may interfere with energy metabolism in the heart by disrupting the energy metabolite-producing activity of mitochondria (reviewed in Cunningham and Spach 1994; Rubin and Doria 1990). Experiments using alcohol-fed hamsters have

Low-density lipoprotein (LDL)—A type of molecule found in the blood composed of a lipid fraction and a protein fraction and that functions as a carrier of cholesterol; LDL has a lower proportion of protein to lipid than does *high-density lipoprotein* (HDL).

Microcirculation—The flow of blood in the microvasculature, the body's system of fine blood vessels.

Myocardium—The heart muscle.

Neurohormones—Hormones formed by certain *neurons* and released by nerve impulses.

Neuron—A nerve cell. Neurons may be classified by function as either sensory neurons, which carry information to the central nervous system, or motor neurons, which carry information away from the central nervous system.

Neurotransmitter—A chemical messenger released by neurons to excite or inhibit adjacent *neurons*.

Organelle—A membrane-surrounded structure found within cells that contains enzymes and other components for performing specialized cell functions.

Phospholipase—Any of a number of enzymes that break down a particular type of chemical bond in *phospholipids*.

Phospholipid—A lipid containing one or more phosphate groups. Phospholipids are major constituents of cell membranes.

Platelet—A disk-shaped structure found in the blood that plays an important role in clotting.

Platelet-activating factor—A substance released by certain types of cells of the immune system that stimulates *platelets*.

Repolarization—The process in which ion fluxes across the cell cause a change in electrical gradient to reestablish polarity (with a negative charge inside and a positive charge outside the cell membrane). See *depolarization*.

Sinoatrial node—The pacemaker of the heart, situated within the right *atrium*. The sinoatrial node generates electrical impulses that cause coordinated contraction of the heart muscle.

Smooth muscle—Involuntary muscle that surrounds and controls the activities of blood vessels and other hollow organs of the body.

Stable angina—*Angina pectoris* occurring in attacks of predictable frequency and duration after exercise, emotional stress, or other circumstances that precipitate increased oxygen demands on the *myocardium*.

Stroke—Any condition leading to partially or completely restricted blood flow to an organ; often used to denote blood loss to the brain. Stroke may be categorized as ischemic, in which blood vessel blockage has an etiology similar to that of CAD, or hemorrhagic, in which bleeding through the vessel wall causes the loss of normal blood flow.

Sympathetic nerve—Nerve of the sympathetic nervous system, which controls automatic processes such as heart rate.

Thrombin—An enzyme that promotes clotting.

Thrombosis—Formation of a *thrombus*.

Thrombus—A blood clot that obstructs a blood vessel.

Ultrastructural—Pertaining to the arrangement of the smallest elements making up the body; that is, structures that are not visible without the use of a microscope.

Vascular—Pertaining to blood vessels.

Vascular resistance—The opposition to blood flow in the blood vessel. Systemic vascular resistance is equal to the blood pressure divided by the *cardiac output*.

Vasodilation—A state of increased blood vessel size.

Ventricular fibrillation—The rapid and uncoordinated contraction of the muscle fibers of the ventricle, a pumping chamber of the heart, resulting in a twitching, rather than contraction, of the ventricle.

shown that 14 weeks of alcohol exposure depresses heart muscle contractility and reduces heart tissue levels of ATP and related high-energy metabolites (Auffermann et al. 1989, 1991). With longer periods of alcohol consumption, metabolite levels normalized but contractility did not; these findings suggest that long-term exposure may result in an adaptive response to alcohol's effects.

Others have shown that basal levels of mitochondrial ATP synthesis are increased in heart cells taken from alcohol-fed rats (Das and Harris 1993). However, these cardiac mitochondria also had a reduced capacity to synthesize ATP in response to an increased energy demand, which suggests that alcohol may impair mitochondrial responsiveness to an increased work load. Related studies have shown that acute administration of alcohol to rats inhibits protein synthesis in cardiac muscle, including a 25-percent decrease in mitochondrial protein synthesis (Siddiq et al. 1993). However, adaptive changes occur with chronic alcohol feeding in rats such that the net rate of protein synthesis in cardiac muscle is close to that of control animals (Preedy and Peters 1990). Cunningham and Spach (1994) recently reported that alcohol alters mitochondrial structure and function in alcohol-fed animals. These changes were less marked with experimental protocols that matched the caloric intake of alcohol-fed and control animals, which suggests an interaction between chronic alcohol consumption and nutritional deprivation in affecting myocardial energy metabolism.

In addition to these direct actions, some of alcohol's effects on the heart are likely to be mediated indirectly through toxic alcohol metabolites. Acetaldehyde reacts chemically with cellular proteins to form adducts that may compromise protein function or stimulate production of autoantibodies, with potential heart tissue pathology (reviewed by Preedy and Richardson 1994). Acetaldehyde may play a role in the alcohol-induced inhibition of cardiac protein synthesis described earlier

(Preedy and Richardson 1994). Alcohol metabolism also generates free radicals that may cause lipid peroxidation, thereby resulting in a loss of cardiac cell viability or damage to heart *microcirculation* (Antonenkov et al. 1989; Hori et al. 1991; Reinke et al. 1987). Alcohol also can be metabolized by an enzyme known as glutathione-S-transferase, which produces *fatty acid ethyl esters* that have deleterious effects on cardiac mitochondria (Lange 1991). In addition, alcohol also may be metabolized to an abnormal *phospholipid*, phosphatidylethanol, by a *phospholipase* normally involved in membrane lipid metabolism and *intracellular signal transduction* (Lindmar and Loffelholz 1992; Panagia et al. 1991). Phosphatidylethanol has a strong tendency to disrupt membrane functions (Omodeo-Salé et al. 1991) and may modify properties of heart cell membranes.

Arrhythmia

The heartbeat is driven by the *sinoatrial node*, a group of intrinsic pacemaker cells in which fluxes of cellular ions initiate electrical *depolarization* of the cell membrane. Once initiated, this depolarization propagates rapidly through the heart to produce an essentially synchronous contraction of the entire organ. The synchronization and frequency of heart muscle contraction are critical for efficient pump function.

Arrhythmias can involve irregular beating (dysrhythmia) or asynchronous contractions of the heart muscle cells (fibrillation). Sustained loss of pump function, particularly that associated with *ventricular fibrillation*, can lead to sudden death. Both acute alcohol intoxication and chronic alcohol consumption are associated with arrhythmias; the most common rhythm disturbances observed are *atrial fibrillation* and ventricular dysrhythmia. In most cases, atrial fibrillation brought on by acute alcohol consumption reverses within 24 hours after drinking stops (Lowenstein et al. 1983).

Alcoholics may have an enhanced sensitivity to short-term arrhythmogenic effects of acute alcohol exposure, and they may experience arrhythmias during alcohol withdrawal (Abbasakoor et al. 1976; Greenspan and Schaal 1983; see Regan 1990, Rubin and Thomas 1992, and Zakhari 1991 for reviews). The term "holiday heart" has been used to refer to arrhythmias associated with binge drinking in alcoholics. Arrhythmia is considered to be one of the major factors precipitating sudden death in alcoholics (Dyer et al. 1980; Regan 1990; Zakhari 1991). A recent survey of 156 published papers demonstrated that heavy drinking is associated with increased risk for *cardiac arrhythmias*, cardiomyopathy, and sudden coronary death (Anderson et al. 1993). Others have reported that electrocardiographic abnormalities in alcoholic patients are associated with an adverse prognosis and indicate dysfunction that may predispose these patients to sudden cardiac death (Day et al. 1993; Yokoyama et al. 1992).

Several potential mechanisms have been implicated in alcohol-induced arrhythmias, including disturbances in the initiation of electrical depolarization, interference in the propagation of electrical impulses, and alterations in the normal path and sequence of electrical excitation. Both acute and chronic alcohol exposure can modify the electrical properties of heart cells responsible for impulse initiation and propagation. Alcohol inhibits the sodium-potassium pump, which is a membrane protein that maintains the basal ion composition inside cardiac cells (McCall and Ryan 1987). Alcohol also modifies the time course of electrical depolarization and subsequent *repolarization* (known as the *action potential*) in atrial and ventricular muscle preparations, including Purkinje fibers (specialized conducting cells of the myocardium) (Carryl et al. 1992; Guarnieri and Lakatta 1990; Patel et al. 1991; Salvatici et al. 1990; Williams et al. 1980). Patterson et al. (1987) have shown that long-term intracoronary alcohol administration results in ventricular arrhythmias accompanied by significant alterations in the electrophysiologic properties of the Purkinje fibers. In contrast, others have found no overt change either in spontaneous beat frequency or in action potential of atria isolated from rats chronically exposed to alcohol, although acute administration of alcohol or nicotine depressed action potentials in these animals (Carpentier and Gallardo-Carpentier 1987; Carryl et al. 1992).

In addition, alcohol may interfere with regulation of heart rate and impulse conduction by *neurohormones* (Carryl et al. 1991; Zakhari 1991). For example, in a canine model, chronic alcohol consumption over a period of 1 year reduced action potential duration and decreased ventricular muscle sensitivity to catecholamines; these changes were associated with an increased vulnerability for ventricular fibrillation (Patel et al. 1991). Finally, it is likely that local myocardial damage induced by alcohol may lead to altered pathways of impulse conduction that can result, among other defects, in abnormal electrical circuits that cause arrhythmia (Zakhari 1991).

The Vascular System

Coronary Artery Disease

The coronary arteries supply blood to the heart muscle and therefore are crucial to the maintenance of cardiac function. CAD results when coronary blood flow is deficient. This most often occurs from narrowing of the blood vessels due to formation of atherosclerotic plaques (*atherosclerosis*), which may be followed by *thrombosis*. Thrombosis causes partial or complete vessel occlusion (Eisenberg 1994). The main clinical manifestations of CAD are *angina pectoris* and acute myocardial infarction (AMI, or heart attack).

CAD is the leading cause of death in Western societies and accounts for about 25 percent of all deaths. Although alcohol has deleterious effects on most aspects of cardiovascular function, many studies have associated alcohol consumption, over a wide range of consumption levels, with reduced risk of CAD (reviewed by Klatsky 1994; McCall 1987). Considerable controversy surrounds these findings, primarily because of the inherent difficulties in controlling for all of the variables that may contribute to CAD risk in the populations studied. In addition, there is concern about how accurately drinkers and nondrinkers were classified in these studies (for example, whether nondrinkers included former drinkers who already were at greater risk for alcohol-induced cardiovascular diseases) (Marmot and Brunner 1991; Shaper 1990).

Nevertheless, the association between alcohol consumption and reduced risk for CAD has been confirmed in numerous studies that have attempted to control for these and other potential confounding factors (Jackson et al. 1991; Klatsky 1994; Klatsky et al. 1990; Rimm et al. 1991). Moreover, most recent studies observe some degree of protection against CAD risk in drinkers versus abstainers that appears to extend across gender and across all age and racial groups so far examined (Garg et al. 1993; Klatsky et al. 1992; Miller et al. 1990).

A key issue in understanding alcohol's role in CAD concerns the amount of alcohol that affords protection. For a broad range of alcohol consumption quantities, the prevalence of nonfatal AMI is greater in abstainers than in drinkers. However, the protective effect of alcohol in CAD mortality is restricted to light to moderate drinkers (Klatsky 1994). The relationship between alcohol quantity and CAD mortality gives rise to a U-shaped curve, with one to two drinks per day associated with reduced mortality risk and abstinence or excessive drinking associated with higher mortality risk. Klatsky (1994) has suggested that increased mortality at higher levels of alcohol intake may represent, in part, deaths from other alcohol-related cardiovascular causes incorrectly attributed to CAD.

However, not all symptoms and consequences of CAD are equally sensitive to the protective effect of alcohol. For example, alcohol may partially mask perception of *angina* but not the pathophysiology associated with *ischemia* (Klatsky 1994). Moreover, alcohol-induced depression of cardiac contractility may enhance chest pain in patients with *stable angina*, due to the resulting decrease in cardiac output (Rubin and Urbano-Marquez 1994). Alcohol also may induce vasospasm—a spasm of muscles in blood vessel walls—which is another factor involved in AMI (Davidson 1989).

Some studies have suggested that specific types of alcoholic beverages may confer greater protective effects than others. Notable in this respect is the so-called French paradox—the observation that despite the prevalence of CAD risk factors (such as high serum cholesterol) in the French population, wine consumption correlates with a markedly lower incidence of CAD (St. Leger et al. 1979). Some evidence indicates lower CAD mortality rates among wine drinkers, and to a lesser extent beer drinkers, compared with drinkers who preferentially consume liquor; however, as yet there is no support for any causal role of beverage type in conferring protection (Klatsky 1994; Klatsky and Armstrong 1993). Other studies have shown no significant difference among beverage types in modifying CAD risk (Klatsky et al. 1990; Rimm et al. 1991; Stampfer et al. 1988).

Several mechanisms have been proposed to explain the effect of light to moderate drinking in reducing CAD risk (reviewed in Klatsky 1994; Sheehy 1992). The strongest evidence favors an increase in blood levels of *high-density lipoprotein* (HDL) cholesterol, which is known as "good" cholesterol. The relationship between CAD and cholesterol/lipoprotein levels is well established, and numerous studies have shown that drinkers have increased HDL levels (Cauley et al. 1987; Diehl et al. 1988; Haskell et al. 1984; Langer et al. 1992; Steinberg et al. 1991), except for patients with severe liver disease (Davidson 1989; Okamoto et al. 1988). Recent large-scale epidemiologic studies that examined various components contributing to alcohol's protective effect in CAD have shown that about one-half of this protection is attributable to increases in HDL cholesterol (Langer et al. 1992; Suh et al. 1992). Others have noted a relationship between alcohol use and elevated levels of *apolipoproteins* associated with the formation of HDL. These apolipoproteins also are closely correlated with reduced risk of CAD (Camargo et al. 1985; Moore et al. 1988; Okamoto et al. 1988).

HDL can be fractionated into different subspecies, such as HDL_2 and HDL_3, and elevated HDL in drinkers may reflect increases in particular subspecies. Both subspecies are elevated in drinkers; HDL_3 is the primary fraction increased in light drinkers (Cauley et al. 1987; Puchois et al. 1990; Razay et al. 1992; Valimaki et al. 1986). HDL_2 has been considered the most protective against CAD, but recent data indicate that both HDL_2 and HDL_3 can have a protective effect (see Davidson 1989; Klatsky 1994).

Another mechanism by which alcohol may help reduce CAD risk is through an *antithrombotic* effect. Blood *platelets* and clotting factors participate in *thrombus* formation (the most common precipitating factor of AMI [Eisenberg 1994]) and may contribute to development of atherosclerosis. Alcohol consumption is associated with a decrease in clotting factor activity and reduced platelet activation (Renaud et al. 1992; Rubin and Rand 1994). In vitro studies show that acute alcohol treatment inhibits platelet activation by stimulatory substances such as *thrombin*, collagen, and *platelet-activating factor*; furthermore, acute alcohol exposure reduces platelet synthesis of thromboxane A_2, which is a type of thromboxane that helps to recruit additional activated platelets to a site of tissue damage. The inhibitory effects of alcohol seem to involve alterations in the intracellular signaling pathways initiated by these stimuli. Important targets for alcohol inhibition in platelets include the thrombin-induced formation of *inositol triphosphate* (Rand et al. 1988) and release of arachidonic acid, which is a precursor of thromboxane A_2 (Rubin 1989; Stubbs and Rubin 1992).

Alcohol consumption is associated with a decrease in clotting factor activity and reduced platelet activation.

Alcohol also has been shown to inhibit platelet thrombus formation in vivo (Rand et al. 1990). This effect mimics the well-established antithrombotic effect of aspirin. However, the agents act through different mechanisms: Alcohol interferes with arachidonic acid mobilization, and aspirin inhibits the subsequent metabolism of arachidonic acid to other biologically active molecules (Benistant and Rubin 1990; Rand et al. 1988). Because they operate through different mechanisms, alcohol and aspirin when used together can prolong bleeding and reduce thrombus formation to a greater extent than either agent alone (Deykin et al. 1982; Keller and Folts 1990).

A third mechanism by which alcohol may protect against CAD involves acetate. This alcohol metabolite increases levels of adenosine, which is a chemical that promotes *vasodilation* (Israel et al. 1994). Adenosine increases coronary blood flow and has a known protective effect against myocardial ischemia (Ely and Berne 1992; Pelleg and Porter 1990). Direct infusion of acetate into isolated animal hearts has been shown to enhance coronary blood flow (Blaise et al. 1989).

Hypertension

Numerous epidemiologic studies associate regular alcohol consumption with elevated blood pressure; this relationship appears to be independent of other known risk factors for hypertension (reviewed by Beilin and Puddey 1992; Davidson 1989; MacMahon 1987). Recent studies have confirmed these findings and also have determined susceptibilities of populations grouped by gender, age, and race (Klag et al. 1990; Moore et al. 1990; Ueshima et al. 1992; Witteman et al. 1990). The studies indicate that alcohol consumption increases the risk of hypertension in men of all age and racial groups. Similar associations have been observed in most studies of women, although studies in the United States indicate that women are less susceptible than men to alcohol's hypertensive effects (Klatsky et al. 1986). In addition, a recent survey in Japan suggested that older women may be less susceptible than men to the hypertensive effects of alcohol consumption (Ueshima et al. 1992).

About one-half of the epidemiologic studies on alcohol and hypertension report that light to moderate drinkers have lower blood pressure than abstainers do (reviewed in Davidson 1989; MacMahon 1987). Overall, however, available epidemiologic data suggest that one to two drinks per day have little effect on blood pressure, and alcohol consumption in excess of two drinks per day is strongly associated with hypertension (Moore et al. 1990; Witteman et al. 1990). Furthermore, hypertension is an important risk factor for other potentially fatal or permanently disabling cardiovascular diseases, including stroke, myocardial infarction, and cardiomyopathy. Thus, alcohol-induced hypertension may be an important contributing factor in other cardiovascular disorders associated with excessive alcohol consumption.

Some researchers suggest that determining the prevalence of alcohol-associated hypertension requires assessment of both the frequency of drinking and the quantity of alcohol consumed (Russel et al. 1991). This finding may reflect, in part, the observation that the action of alcohol on blood pressure is largely due to very recent alcohol consumption and is rapidly reversible (in drinkers, hypertension appears to reverse within 2 to 3 weeks of reducing alcohol intake) (Maheswaran et al. 1991, 1992; Ueshima et al. 1993).

Different mechanisms have been postulated to explain how alcohol consumption causes hypertension (reviewed in Beilin and Puddey 1992; Zakhari 1991). In vivo, regulation of blood pressure involves a complex array of interacting factors (figure 3). Alcohol modifies the secretion of many hormones and *neurotransmitters* that regulate cardiac and vascular function; consequences of these effects may be alterations in heart rate, force of contraction, *vascular resistance*, and distribution of blood flow. In addition, repeated episodes of alcohol's acute effects may yield adaptive changes with deleterious consequences. Studies in alcohol-fed rats have shown that an increase in *sympathetic nerve* activity (which stimulates the heart) contributes to alcohol's hypertensive effect (Russ et al. 1991). Other investigators report that alcohol decreases the sensitivity of *baroreceptors*, which are sensory *neurons* that perceive increases in pressure within the chambers of the heart and major vessels to regulate heart rate and vascular resistance (Abdel-Rahman and Wooles 1987; el-Mas and Abdel-Rahman 1993).

Another potential mechanism for alcohol-induced hypertension may involve a direct effect on contractile properties of vascular *smooth muscle* (Zakhari 1991). Acute alcohol administration reduces intracellular calcium levels, thus resulting in relaxation of rat aortic tissue (Zhang et al. 1992). In contrast, chronic alcohol exposure increases calcium flux into rat aortic smooth muscle cells (Vasdev et al. 1991). These data suggest that chronic alcohol exposure may lead to adaptive changes that affect regulation of vascular muscle contraction.

Of interest is a possible relationship between alterations in calcium fluxes and *hypomagnesemia* (magnesium deficiency) observed in alcoholics (Altura and Altura 1994). Depletion of cellular magnesium may enhance calcium entry into the blood vessels of muscle cells, thereby resulting in vasoconstriction (Altura and Altura 1994). In laboratory animals, magnesium supplementation has been shown to prevent alcohol-induced hypertension (Hsieh et al. 1992), and evidence from at least one epidemiologic study in humans suggests that increased magnesium intake may help reduce risk of hypertension (Ascherio et al. 1992). Magnesium deficiency in rats also has been reported to cause a predisposition to oxidative injury in heart tissue after ischemia (Kramer et al. 1994). In isolated perfused rat hearts, alcohol treatment has been shown to induce loss of cellular magnesium (Jelicks and Gupta 1991–92), and high levels of magnesium have been shown to have a protective effect against the acute cardiotoxic effects of alcohol (Zou et al. 1991).

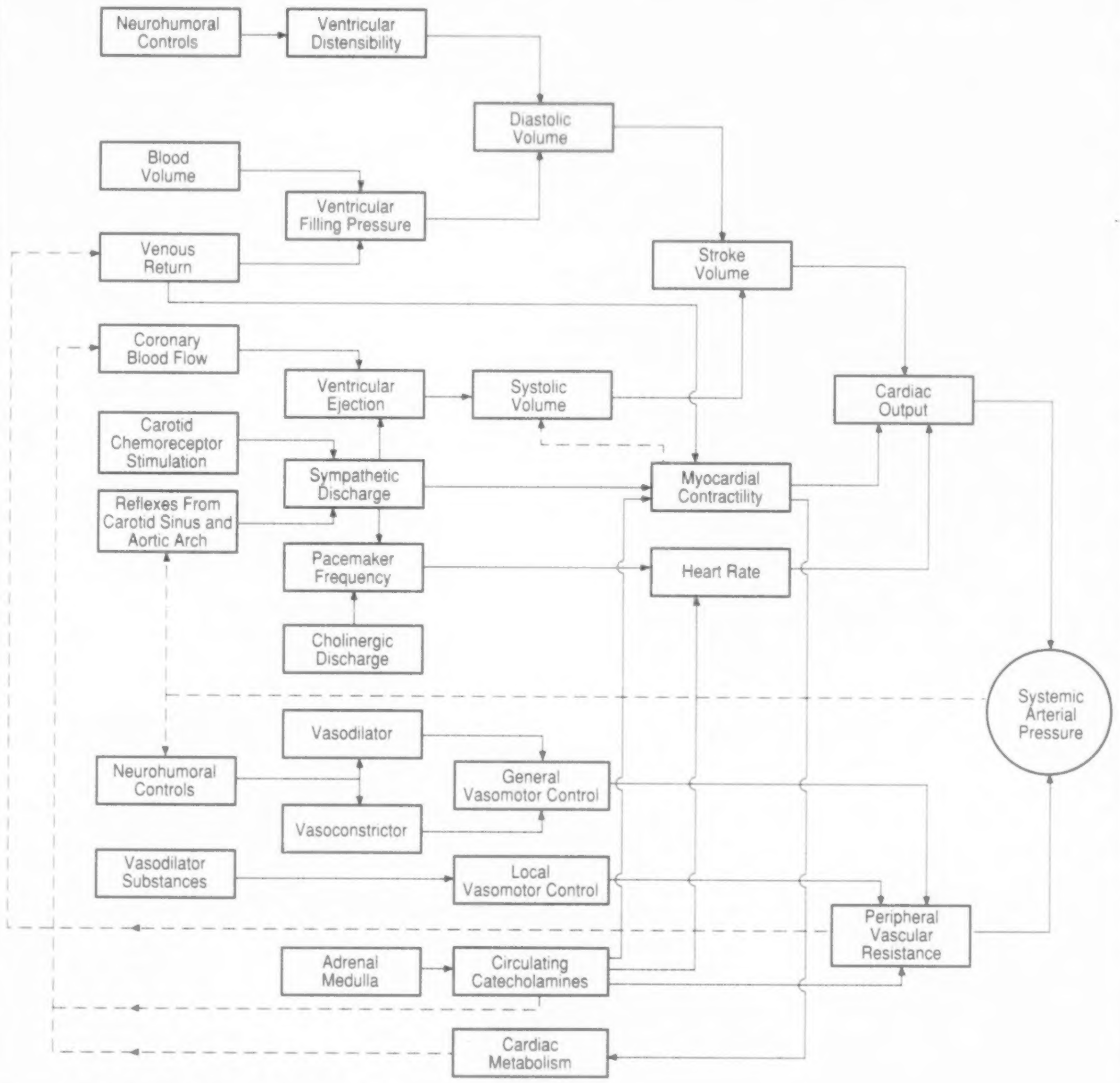
Stroke

Cerebrovascular disease refers to conditions giving rise to inadequate blood supply to the brain (analogous to the disruption of blood flow to heart muscle in CAD). Sudden, severe interruption of cerebral blood supply results in stroke. Stroke may be categorized as ischemic, in which blockage of a blood vessel has an etiology similar to that of CAD, or hemorrhagic, in which bleeding through the vessel wall causes the loss of normal blood flow. There is a clear association between heavy alcohol consumption and an increased incidence of stroke (reviewed in Anderson et al. 1993; Davidson 1989; Regan 1990). Because alcohol may attenuate coronary atherosclerosis, some investigators have suggested that light alcohol consumption has a protective effect against ischemic stroke (Gorelick 1989; Gorelick and Kelly 1992; Klatsky et al. 1989). However, alcohol's potential antithrombotic effects might be expected to enhance risk for hemorrhagic stroke.

Epidemiologic studies have shown that the incidence of both ischemic and hemorrhagic stroke is lower in light drinkers than in nondrinkers (Gill et al. 1991; Jamrozik et al. 1994; Palomaki and Kaste 1993; Rodgers et al. 1993). The studies revealed U- or J-shaped relationships between amount of alcohol consumed and relative risk of stroke and also indicated that an alcohol consumption level of one to two drinks per day decreases stroke incidence by as much as 50 percent. Nevertheless, these and other studies have shown that higher levels of alcohol consumption universally increase risk of stroke (Anderson et al. 1993; Shaper et al. 1991). Consumption of five or more drinks per day increases risk of stroke by 250 to 450 percent (Gill et al. 1991; Palomaki and Kaste 1993; Rodgers et al. 1993).

Figure 3. The complex array of factors that affect blood pressure.

In chronic alcoholics, alcohol may interact with any of these factors to bring about hypertension.


Neurohumoral Controls
Ventricular Distensibility
Diastolic Volume
Blood Volume
Ventricular Filling Pressure
Venous Return
Stroke Volume
Coronary Blood Flow
Ventricular Ejection
Systolic Volume
Cardiac Output
Carotid Chemoreceptor Stimulation
Sympathetic Discharge
Myocardial Contractility
Reflexes From Carotid Sinus and Aortic Arch
Pacemaker Frequency
Heart Rate
Cholinergic Discharge
Systemic Arterial Pressure
Vasodilator
Neurohumoral Controls
General Vasomotor Control
Vasoconstrictor
Vasodilator Substances
Local Vasomotor Control
Peripheral Vascular Resistance
Adrenal Medulla
Circulating Catecholamines
Cardiac Metabolism

Source: Zakhari 1991. Reprinted by permission.

Several aforementioned cardiovascular effects of alcohol are also known risk factors for stroke. In particular, the relationship between hypertension and stroke is well known. Also, alcohol's ability to interfere with blood clotting may contribute to an increased likelihood of hemorrhage. A further contributing factor may be alcohol-induced cerebrovasospasm, which is a local contraction of the blood vessel walls in the brain that can severely restrict or even block blood flow. Animal studies have provided direct evidence for alcohol-induced vasocontraction leading to brain ischemia (Barbour et al. 1993). Related studies have demonstrated that alcohol treatment results in loss of cellular magnesium in cultured cerebral vascular muscle cells (Altura et al. 1993) and that alcohol intoxication causes a loss of free magnesium in the brain (Altura et al. 1991–92).

Risk-Benefit Factors

Germane to this discussion are the risk-benefit factors of alcohol for the cardiovascular system. As discussed earlier, light to moderate drinking may reduce risk for death due to CAD and perhaps to stroke. However, it is also clear that higher levels of alcohol consumption are associated with greatly enhanced risk for stroke and increase risk for sudden death from cardiovascular causes (Anderson et al. 1993; Castelli 1990; Wannamethee and Shaper 1992); the possibility that regular consumption of low levels of alcohol has harmful outcomes for other cardiovascular diseases cannot be excluded. Moreover, regular alcohol use has other detrimental health and social consequences that should be balanced against its potential benefits. Finally, current evidence clearly demonstrates harmful effects of moderate to heavy alcohol consumption on the cardiovascular system. A recent review of 156 papers concerned with alcohol consumption and risk for cardiovascular and other diseases has shown that at levels of alcohol consumption of more than 20 to 30 grams (approximately two drinks) per day, all individuals are likely to accumulate some risk of harm (Anderson et al. 1993). Taken together, available information indicates that an upper limit of one to two drinks per day is probably consistent with sustained cardiovascular health (Anderson et al. 1993; Goldberg et al. 1994).

> *An upper limit of one to two drinks per day is probably consistent with sustained cardiovascular health.*

Alcohol-Related Neuropsychological Disorders

Alcohol and its metabolites can cause direct or indirect damage to nervous tissues; furthermore, alcohol-induced damage to other body organs (such as the liver) can in turn interfere with normal nerve function (Charness 1993; Lovinger 1993). Prolonged alcohol abuse is associated with brain damage and corresponding changes in mental functioning. Brain imaging techniques have provided evidence that alcoholism causes structural brain changes (Jernigan et al. 1991*a*; Pfefferbaum et al. 1992). Neuropsychological tests have helped characterize the impaired mental processes that accompany alcoholism (Spreen and Strauss 1991).

One of the most serious neurological outcomes of alcoholism is Korsakoff's syndrome, which is characterized by memory deficits, most notably anterograde amnesia (an inability to remember new information for more than a few seconds), and numerous other *cognitive* impairments. Despite these deficits, the patients' intellectual abilities, as measured by intelligence quotient (IQ) tests, remain relatively intact because much of the information and ability assessed by IQ tests is acquired in the distant past and because patients with Korsakoff's syndrome (Korsakoff patients) usually can retain memories formed before the onset of prolonged heavy drinking.

Over the past 25 years, clinical and experimental research has documented cognitive deficits in alcoholics with and without Korsakoff's syndrome. Such deficits include retarded information processing; poor attention; difficulties with *abstraction*, solving problems, and learning new information; emotional abnormalities and *disinhibitions*; and reduced *visuospatial abilities* (the capacity to organize and analyze objects in two- or three-dimensional space) (Ellis and Oscar-Berman 1989; Parsons and Nixon 1993; Salmon et al. 1993). This section reviews the techniques used to examine neurocognitive deficits and the evidence documenting relationships between alcohol abuse, structural brain damage, and associated neuropsychological consequences.

Alcohol-Related Structural Brain Damage and Associated Neuropsychological Changes

Structural damage to brain tissue can be determined based on neuropathological evidence from post mortem examination of the brain's component parts and individual nerve cells. Brain tissue damage also can be assessed in vivo based on *neuroradiological* evidence from brain imaging techniques, such as *magnetic resonance imaging* (MRI) and *computerized tomography* (CT), that allow the brain to be viewed inside the skull. Other evidence can be obtained with functional imaging or *electrophysiologic techniques*. Functional brain imaging techniques, such as *positron emission tomography* (PET), detect variables such as the regional distribution of blood flow and glucose metabolism within selected areas of the brain. Electrophysiologic techniques such as *event-related potentials* (ERPs) measure the electrical activity of groups of nerve cells in various parts of the brain. Information using functional imaging and electrophysiologic techniques can be translated into meaningful pictures that allow observation of the brain during thinking processes or task performance.

In studies of alcoholics, such procedures have provided evidence of abnormal brain functioning and brain shrinkage. Regions especially vulnerable to damage, with resulting impairment in mental functioning, include the cerebellum, limbic system, diencephalon, and regions of the cerebral cortex (Charness 1993; Lishman 1990) (see figure 4 and later discussion for descriptions of these and other brain regions). Importantly, because innumerable neuronal pathways interconnect these and other areas of the brain, damage to one structure or system may affect another structure or system.

In alcoholics, damage to the cerebellum results in loss of motor coordination, which is manifested as lurching and staggering. Although alterations in cerebellar structure in alcoholics are well documented, little is known about the mechanisms linking these changes to movement disorders (see Pentney 1993 for a review). The focus of the present discussion is on the somewhat better characterized changes observed in the limbic system, diencephalon, and regions of the cerebral cortex.

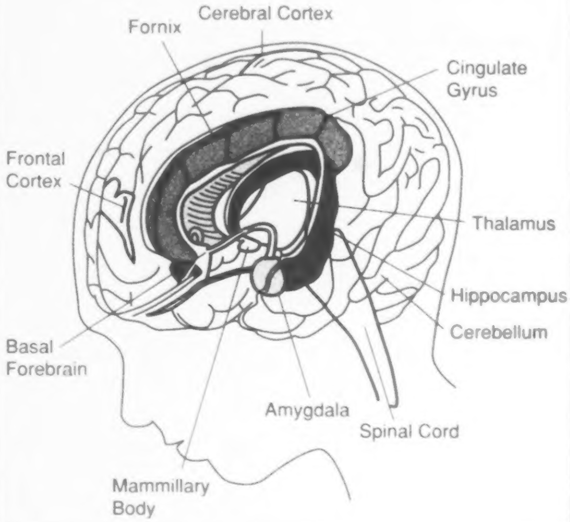
The Limbic System

The limbic system comprises a network of structures located deep within the brain and includes the hippocampus, cingulate gyrus, and amygdala (Martin 1989). Limbic system activities are critical to memory formation, emotional functioning, olfaction, and the integration of information perceived through the various senses. Deficits in all of these functions have been observed in alcoholics, and memory loss similar to the amnesia observed in alcoholic patients with Korsakoff's syndrome has been associated with damage to the hippocampus and the amygdala (Petri and Mishkin 1994).

A recent study of alcoholic patients with and without Korsakoff's syndrome examined their abilities to recognize and identify emotional states from facial expressions and verbal assertions (Oscar-Berman et al. 1990*a*). As stimuli to test emotional functioning, the researchers used photographs of facial expressions conveying four emotions (happiness, sadness, anger, or neutrality) and recordings of sentences having intonations or semantic meanings conveying the same four emotions. In Korsakoff patients, significant deficits were observed in visual and auditory emotional perception and memory: Patients generally made fewer correct identifications and had poorer memory for the stimuli than age-matched nonalcoholic and alcoholic control subjects did. Only minor deficits were observed in non-Korsakoff alcoholics.

Figure 4. The human brain.

Among brain structures most frequently implicated in alcohol-related neurological disorders are the cerebral cortex, parts of the limbic system (especially the hippocampus and amygdala), parts of the diencephalon (especially the mammillary bodies) of the hypothalamus and a portion of the thalamus known as the dorsomedial thalamic nucleus, and several central neurotransmitter systems found in the basal forebrain.



Another study of limbic system function applied a standardized, multiple-choice, scratch-and-sniff test to determine smell identification abilities in Korsakoff patients in conjunction with MRI measures to detect *cortical* and *subcortical* changes (Shear et al. 1992). The researchers found impairments in olfactory functioning that were associated with volume loss in specific cortical and subcortical brain regions, several of which are part of the limbic system or have direct limbic system connections.

In a study of cross-modal functioning—an aspect of sensory integration described as the ability to use one *sensory modality* (such as vision) to learn something in another sensory modality (such as touch)—alcoholics with and without Korsakoff's syndrome were taught to choose specific forms or textures that they could see but not touch or touch but not see. Subjects were then asked to recognize the visual cues by touch alone and the tactual cues by sight alone. In Korsakoff patients, these tests revealed significant cross-modal impairments attributable to damage to the limbic system and func-

Glossary

Abstraction—Mental function that involves forming concepts, solving problems, and thinking flexibly.

Acetylcholine—A *cholinergic neurotransmitter* that is critical to memory. Acetylcholine is derived from choline, a vitamin of the B complex, and is essential for transmission of nerve impulses.

Catecholaminergic—Activated by or secreting catecholamines.

Cerebral cortex—The layer of gray matter covering the surface of each cerebral hemisphere; responsible for the higher mental functions, general movement, visceral functions, perception, and behavioral reactions as well as for the association and integration of these functions.

Cerebrum—The largest portion of the brain, including the cerebral hemispheres; controls consciousness and voluntary body functions.

Cholinergic—Pertaining to nervous system activity stimulated, activated, or transmitted by *acetylcholine*.

Cognitive—Pertaining to cognition, which describes those brain activities that involve all aspects of perceiving, thinking, and remembering.

Computerized tomography (CT)—A technique for recording internal body images of a tissue or organ, such as the brain, that uses x-ray bombardment to yield a three-dimensional picture.

Cortical—Pertaining to the *cerebral cortex*.

Cortisol—A steroid hormone that affects metabolism of glucose, proteins, and fats and has many other functions.

Dichotic listening tasks—Tasks involving listening to two different sounds entering both ears at the same time. The sounds are preselected and precisely controlled, and responses to these stimuli are used to determine similarities and differences in left and right hemisphere function.

Disinhibition—The removal of inhibitions, as occurs with reduction of inhibitory function of the *cerebral cortex* by drugs such as alcohol.

Electrophysiologic techniques—Techniques used to measure patterns and production of electrical activity in the body, particularly in the nervous system, and their effects.

Event-related potentials (ERPs)—Neuroelectrical activities that serve as sensitive indicators of the brain's responsiveness to visual, auditory, olfactory, and other stimuli.

Fissure—A deep fold forming a cleft or groove in the *cerebral cortex* that involves the entire thickness of the brain wall.

Hepatic encephalopathy—A progressive metabolic liver disorder that affects intellectual functioning and is characterized by disturbances of consciousness that may progress to psychiatric changes or coma.

Locus coeruleus—A structure that produces catecholamines, located in the stalk-like portion of the brain (the brain stem) that connects the cerebral hemispheres with the spinal cord.

Magnetic resonance imaging (MRI)—A method for visualizing soft tissues (such as neural tissues) by applying an external magnetic field and observing the magnetic properties of certain atoms and their interaction with radio waves to reveal the structural milieu of these atoms. The shape of the tissues can then be reconstructed by integrating this structural information in three dimensions.

Neuroradiological—Pertaining to radiology of the nervous system; that is, the study of the nervous system by use of radiant energy or radioactive substances. Neuroradiological techniques include *magnetic resonance imaging, computerized tomography*, and *positron emission tomography*.

Neurotoxicity—The quality of being destructive or poisonous to nervous tissue.

Neurotransmitter—A chemical messenger released by neurons to excite or inhibit adjacent neurons.

Perceptual asymmetry—Uneven ability of the left and right cerebral hemispheres to process information from left- and right-sided sensory input; for example, as perceived through the eyes or ears.

Periventricular—Near the ventricles, fluid-filled cavities of the brain.

Positron emission tomography (PET)—A technique that detects signals generated by the collision of positrons (positively charged electrons) with electrons. Positrons are emitted by certain radioisotopes introduced into the body. The signals are used to generate an image of local metabolic and physiologic functions in tissues, such as glucose metabolism or blood flow in the brain.

Sensory modality—A specific sensory entity, such as vision or taste.

Serotonergic—Activated by or containing *serotonin*.

Serotonin—A primary central nervous system *neurotransmitter* that stimulates target neurons.

Spatial memory—Memory for nonverbal information perceived in the environment.

Subcortical—Pertaining to brain structures beneath the *cerebral cortex*.

Sulci—Grooves found on the surface of the brain.

Tactual learning—Learning based on perception, through touch, of texture and form.

Temporal lobe—The lower lateral lobe of the cerebral hemisphere.

Visuospatial ability—The capacity to organize and analyze objects in three-dimensional space.

tionally related regions of the cerebral cortex; only minor alterations were observed in non-Korsakoff alcoholics (Oscar-Berman et al. 1990*b*).

The Diencephalon

The diencephalon, a region nestled in the center of the brain, acts as a way station for outgoing and incoming nerve signals of many other areas of the brain. The diencephalon's role in memory functioning is not clearly understood. The main diencephalic areas implicated in memory functioning are the mammillary bodies of the hypothalamus, a portion of the thalamus known as the dorsomedial thalamic nucleus, and the nerve fibers connecting these two structures. These areas have been singled out for study because of their anatomical connections with the hippocampus and amygdala and because diencephalic structural damage has been observed in many memory-disordered patients (Victor et al. 1971, 1989). In a more recent study, Jernigan et al. (1991*b*) found that alcoholics with Korsakoff's syndrome could be differentiated from those without it based on changes in diencephalic gray matter (clusters of nerve cell bodies): The former group had a greater reduction in gray matter volume in the anterior diencephalon. However, another study that compared MRI measures of these brain regions in alcoholics with and without the amnesia of Korsakoff's syndrome (Blansjaar et al. 1992) found diencephalic shrinkage at similar frequencies in both groups. The investigators suggested that diencephalic lesions develop with alcoholism, regardless of whether patients progress to Korsakoff's syndrome, and likely are common features of chronic alcoholism and malnutrition (discussed later) rather than typical of Korsakoff's syndrome per se.

Alcoholics may develop neurocognitive deficits suggestive of generalized cortical atrophy. They also may have deficits in spatial memory and tactual learning.

The Cerebral Cortex

Neuroradiological evidence (Adams et al. 1993; Erbas et al. 1992; Gilman et al. 1990; Jernigan et al. 1991*a,b*; Pfefferbaum and Rosenbloom 1993; Volkow et al. 1992; Wang et al. 1992) as well as post mortem analyses (Harper and Kril 1993; Harper et al. 1990; Jensen and Pakkenberg 1993) have revealed structural changes in the brains of alcoholics. These changes include enlargement of the ventricles (fluid-filled cavities inside the brain) and widening of the *fissures* and *sulci* (grooves between the folds on the brain's surface) over the cerebral hemispheres, both of which suggest cortical atrophy (Pfefferbaum et al. 1992). A study by Jernigan et al. (1991*b*) compared alcoholics with and without Korsakoff's syndrome and revealed that the former had both greater ventricular size and smaller gray matter volume in particular regions within the cortex in addition to the reductions in subcortical (diencephalic) gray matter noted previously. Post mortem pathology in alcoholic brains indicates reductions in cerebral cortex volume (Harper and Kril 1993); most of this tissue loss was explained as a reduction in the volume of cerebral white matter (nerve fibers). However, shrinkage of cortical gray matter also was observed, and loss of cortical neurons was especially evident in parts of the frontal lobes (Harper and Kril 1993).

Alcoholics also may develop neurocognitive deficits suggestive of generalized cortical atrophy. Chronic alcoholics have difficulty on tests of problem solving (Beatty et al. 1993; Braun and Richer 1993; Nixon et al. 1992; Sullivan et al. 1993) and in forming visual associations (Bowden et al. 1992). They also may have deficits in *spatial memory* (Bowden and McCarter 1993; Joyce and Robbins 1991; Oscar-Berman et al. 1992; Verfaellie et al. 1992) and *tactual learning* (Oscar-Berman et al. 1990*b*). All of these deficits are consistent with cortical damage.

Neuropsychological studies also have shown that Korsakoff patients exhibit clinical signs associated with damage to the frontal cortex (Joyce and Robbins 1991); for example, emotional apathy, disinhibition, poor judgment and planning ability, and abnormal response perseveration (the unwanted repetition of a previous response or inappropriate behavior). Research in monkeys using visual and auditory delayed-response tests highly sensitive to frontal lobe damage strongly suggests frontal system dysfunction in alcoholic Korsakoff's syndrome (Oscar-Berman et al. 1992; see Oscar-Berman and Hutner 1993 for a review).

Neuropsychological approaches have been combined with brain imaging and functional imaging approaches to evaluate relationships between sites of alcohol-induced damage and the nature of cognitive decline. One recent study in chronic alcoholics found little evidence to correlate changes in gray matter structures with performance on neuropsychological tests but observed correlations between measures of cortical and ventricular fluid volume changes and certain cognitive measures (Jernigan et al. 1991*a*). Wang et al. (1993*b*) combined MRI and functional imaging techniques (including PET) with behavioral measures in a study of chronic alcoholics. The researchers noted associations between the degree of cortical shrinkage (indicative of minor structural changes) and decreased brain glucose metabolism (suggesting a loss of brain tissue). They also observed associations between performance on certain neuropsychological tests and decreased frontal lobe glucose metabolism but found no correlation between brain structural changes and neuropsychological test performance. These results were thought to reflect either the preservation of cognitive abilities even with minor changes in brain structure or the insensitivity of the tests used to detect structural changes.

A similar study of 40 chronic alcoholic patients combined CT scans and cerebral blood flow measures with neuropsychological tests (Nicolas et al. 1993). This study revealed significant brain hypoperfusion (reduced blood flow) in 26 of these patients but cerebral shrinkage (mainly in the frontal lobes) in only 11. Twenty-nine of the 40 patients also exhibited significant impairment on tests of frontal lobe functioning and visuospatial skills; these frontal lobe defects were independently related to both frontal lobe shrinkage and hypoperfusion.

Significant blood flow reductions also have been observed in certain regions of the cerebral cortex of alcoholic men.

Erbas et al. (1992) observed decreased cerebral blood flow (mostly in frontal regions) in 85 percent and structural changes, based on CT measures, in 60 percent of alcoholics. Significant blood flow reductions also have been observed in certain regions of the cerebral cortex of alcoholic men (Melgaard et al. 1990). When these alcoholics were divided into two groups based on the severity of alcohol abuse, the alcoholics who were more severe abusers had greater blood flow reductions in frontal cortical and periventricular regions than the alcoholics who were less severe abusers. When alcoholics were divided into two groups based on severity of their intellectual impairment, the more impaired group showed greater blood flow reduction in frontal cortical and *periventricular* regions, as well as in the cortical regions of the *temporal lobes*, than the less impaired group did.

Similar studies have shown significant correlations between reductions in glucose metabolism in the frontal lobe and errors on a test of frontal lobe function, as well as between decreased cerebral glucose metabolism and shrinkage of the medial frontal cortex as identified on CT or MRI scans (Adams et al. 1993; Gilman et al. 1990). Collectively, these findings support associations between alcoholism and impaired metabolic and neuropsychological functions of the frontal cortex.

Korsakoff patients also exhibit reductions of blood flow in the frontal areas of the *cerebrum*. In addition, the degree of flow reduction can be correlated with the degree of impairment seen on tests of memory and orientation (with less flow corresponding to increased impairment) (Hunter et al. 1989). Such metabolic deficits may result from a reduction in neuronal activity of normal tissue mass, a reduction of tissue mass having normal neuronal activity, or both (Hunter 1990; Wang et al. 1993*b*). In view of CT and neuropathological studies identifying gray and white matter loss in the frontal lobes of Korsakoff patients, Hunter's findings of metabolic impairment in this region are consistent, at least in part, with reduced tissue mass (Hunter 1990).

Although S.S. Korsakoff (the Russian scientist who first characterized Korsakoff's syndrome) observed pathology in the cerebral cortex, his description of the disease was concerned largely with neuropsychological characteristics in association with various possible etiologies (Victor and Yakovlev 1955). The brain structures involved were not implicated until much later by investigators such as Brion (1969) and Victor et al. (1971), who implicated diencephalic damage and used neuropsychological criteria to classify their patients' problems. Whether the critical lesions site(s) in Korsakoff's syndrome is cortical, diencephalic, or both remains an area of controversy, and definitive diagnosis requires both neuropsychological and neuropathological evidence.

Impairments in Neurotransmission

Neurons communicate with one another through the release and uptake of neurotransmitters. Among many different activities, neurotransmitters play significant roles in memory functioning. The neurotransmitters thought to be most important in memory include those of the *cholinergic*, *catecholaminergic*, and *serotonergic* systems.

Acetylcholine, a cholinergic neurotransmitter considered critical to memory, is produced in many sites, including the nucleus basalis of Meynert, a region located within the basal forebrain (see figure 4). The nucleus basalis of Meynert communicates with other brain regions (such as the hippocampus and cerebral cortex) implicated in alcohol-related neuropsychological decline. Acetylcholine deficiency in the basal forebrain has been linked to memory disturbances in alcoholic Korsakoff's syndrome (Arendt 1993). In a related study, administration of anticholinergic drugs to healthy subjects produced temporary cognitive deficits that resemble Korsakoff's amnesia (Kopelman 1985).

Korsakoff patients also have reduced cerebrospinal fluid levels of catecholamine metabolites that correlate with memory loss. Administration of catecholaminergic agents appears to facilitate memory processing in these patients by increasing attention (see Martin and Nimmerrichter 1993 for a review). However, in these patients, post mortem examination of the *locus coeruleus*—a brain stem structure that produces catecholamines—has revealed no significant cellular pathology to implicate it as a critical lesion site in Korsakoff-associated amnesia (Halliday et al. 1992).

Administration of serotonergic agents facilitates memory processes in some impaired alcoholics and in Korsakoff patients (Martin et al. 1995; Martin and Nimmerrichter 1993). Degeneration has been shown in *serotonin*-producing neurons of the brain stem in alcoholics, but this pathology was evident regardless of history of memory impairment (Halliday et al. 1993). Thus, alcohol-associated damage to serotonergic neurons may not contribute to memory impairment.

Clearly, future research is needed to elucidate the role of alcohol-induced neurotransmitter impairment in memory and other cognitive functions. These studies may help direct strategies for treatment of alcohol-related neurological disorders and will provide clues about the structures and mechanisms involved in normal and abnormal memory processes.

Variables Influencing Development of Alcohol-Induced Brain Damage

Alcoholism is a multidimensional disorder. Likewise, alcohol-related neurobehavioral consequences are complex, and individual differences are prevalent. According to one estimate, between 50 and 85 percent of non-Korsakoff alcoholics exhibit signs of cognitive decline (Parsons 1993); among those with deficits, researchers have yet to identify determinants of alcohol consumption (such as duration, frequency, or quantity of drinking) that consistently correlate with neuro-psychological impairment. However, in general, the greater the alcohol intake, the poorer the performance on cognitive tasks (Parsons 1993).

The differences observed suggest that a variety of factors may contribute to an alcohol-related cognitive decline. A current focus of research aims to identify factors that explain the propensity of some alcoholics, but not others, to develop specific neurological or mental changes. Possible candidates include alcohol-associated health or nutrition problems, patterns of drinking, gender, age at which problem drinking begins, heritable factors, and number of repeated incidences of withdrawal.

Alcohol-Related Pathologies That May Affect Brain Function

Many alcoholics suffer from vitamin deficiency and liver disease. Both conditions can produce metabolic and physiologic changes that may adversely affect neurological function and that also may interact with alcohol to cause damage to the nervous system.

Malnutrition is common among alcoholics, in part because chronic drinking suppresses appetite and interferes with digestive processes and the absorption of nutrients (Lieber 1989). Prolonged drinking with improper diet may result in thiamine (vitamin B_1) deficiency, which has long been associated with the neuropathology of alcoholic Korsakoff's syndrome (Butterworth et al. 1993; Victor et al. 1971). Some researchers have proposed that diencephalic damage in Korsakoff patients can be attributed to thiamine deficiency, whereas cortical abnormalities, particularly in the frontal lobes, result from alcohol *neurotoxicity* or other conditions associated with alcoholism (such as liver disease or head trauma). For example, Joyce (1994) states that although alcohol can damage cortical neurons and contribute to cognitive impairment, thiamine malnutrition affecting the diencephalon can account for all clinical forms of brain damage in alcoholics whether the patients have minimal cognitive impairments, amnesia, or dementia.

In contrast, Lishman (1990) suggests that alcoholics can be divided into distinct subgroups according to different vulnerabilities to alcohol-induced brain damage. These vulnerabilities derive from two distinct pathological processes thought to operate independently in some people and to interact in others. The first process, characterized on brain scans as shrinkage of the cerebral cortex and possible atrophy of basal forebrain regions, is thought to result from the direct neurotoxic effects of alcohol. The second process, characterized by damage to the diencephalon, is attributed to thiamine deficiency, which may cause blood vessels to rupture in that region. Alcoholics who are susceptible to alcohol neurotoxicity alone may develop permanent or transient cognitive deficits associated with cortical shrinkage (Jacobson et al. 1990), whereas those susceptible to thiamine deficiency alone may develop a mild or transient Korsakoff state with anterograde amnesia as a salient feature. Alcoholics who are vulnerable to both forms of pathology may develop widespread damage to large regions of the cerebral cortex and structures deep within the brain (Lishman 1990); these people will exhibit severe anterograde amnesia and other cognitive impairments (Jacobson and Lishman 1990).

Alcohol-related liver disease also contributes to neurological disturbances associated with heavy drinking (Tarter et al. 1993). The risk of alcoholic liver damage depends on factors such as gender, nutrition, and the quantity and pattern of alcohol consumed. *Hepatic encephalopathy*, a progressive metabolic liver disorder that affects intellectual functioning, may be reversible with treatment of liver disease or liver transplant (Tarter et al. 1993). Recent research has focused on biological factors involved in protecting liver cells from alcohol's direct and indirect toxic effects; chronic alcohol exposure appears to impair these protective mechanisms (Diehl 1993).

Gender

Although some research supports gender-related differences in alcohol-mediated neuropsychological deficits, there is controversy as to whether or to what extent such differences exist (see Glenn 1993 and Nixon 1993 for a review). Studies using electrophysiologic, imaging, and neuropsychological measures have yielded contradictory results. For example, Parsons (1994) has reported that although both male and female alcoholic subjects showed impaired neuropsychological performance relative to same-gender control subjects, only male alcoholics differed from control subjects on measures of brain electrical activity. In contrast, another study demonstrated electrophysiologic abnormalities in female alcoholics that are similar to those of male alcoholics (Hill and Steinhauer 1993).

Some studies suggest that women are more vulnerable than men to alcohol-associated neuropsychological deficits. Using CT brain scans, Lishman et al. (1987) found that female alcoholics had larger ventricles (reflecting brain shrinkage) than same-gender nonalcoholic control subjects did; this size difference was greater than that observed between alcoholic males and same-gender nonalcoholic control subjects. Lishman et al. (1987) also observed similar degrees of impairment on tests of mental functioning in male and female alcoholics even though female alcoholics had shorter drinking histories, had consumed less alcohol, and had been abstinent for longer periods of time than male alcoholics. Another study compared CT brain scans of alcoholic men and women before and after treatment for alcoholism (Mann et al. 1992). The investigators found similar degrees of brain shrinkage despite significantly shorter drinking histories in the women, even after controlling for moderating variables such as age, daily alcohol consumption, and liver dysfunction. These findings and those of Lishman et al. (1987) indicate that women may be more sensitive to the neuropsychological complications of alcoholism. However, whereas MRI findings have shown that alcoholic men have enlarged ventricles relative to age-matched nonalcoholic men (Zipursky et al. 1989), MRI findings for women have revealed no differences in ventricular volume related to alcoholism (Kroft et al. 1991).

Gender differences in alcohol's effects on brain structure should, in theory, be reflected as alterations in neuropsychological function. One approach to characterizing such differences is to identify differences in asymmetric patterns of left and right hemisphere function, also known as cerebral laterality patterns.

Early in fetal development, gender differences (sexual dimorphisms) arise in brain organization that are, in part, due to the presence of testosterone in males but not in females (Geschwind and Galaburda 1985). Among these gender differences are variations in cerebral laterality patterns (Halpern 1992). Sexual dimorphism in asymmetric brain functions may predispose differences in *perceptual asymmetries* and other neuropsychological responses to alcohol (see Lancaster 1994 for a review).

The brains of both men and women have asymmetrical abilities to process verbal and nonverbal information. The left hemisphere usually is more efficient with verbal signals, such as words and phrases; the right hemisphere is more efficient with nonverbal signals, such as music. Based on evidence (from a separate line of research) of right hemisphere dysfunction in alcoholics, investigators have expected to find alterations in cerebral laterality patterns. A variety of studies have examined cerebral laterality patterns in alcoholics by using tests of visual, tactual, and auditory functions. However, most studies have relied on male subjects and have revealed few consistent patterns of abnormalities (reviewed by Oscar-Berman 1988, 1992).

One exception is a study by Drake et al. (1990), who have characterized gender differences by using *dichotic listening tasks* sensitive to left and right hemisphere functioning. The researchers compared alcoholic men and women with nonalcoholic control subjects based on their ability to identify competing verbal or nonverbal signals. The signals were presented as a series of two words or two melodies through stereo headsets. Drake et al. (1990) found that male alcoholics showed atypical laterality patterns, which were characterized as a larger left hemisphere advantage for identifying words and a smaller right hemisphere advantage for identifying melodies. In contrast, female alcoholics' laterality patterns did not differ from those of control subjects on either dichotic listening task. These results were interpreted as evidence for right hemisphere dysfunction in male but not female alcoholics. Asymmetric brain function in alcoholics is likely to become an increasingly active area of study, particularly with regard to studies of women.

Age

Alcoholism has been associated with premature aging of the brain. Evidence for this hypothesis of premature aging has come from studies of brain imaging, neuropathology (Courville 1966; Pfefferbaum et al. 1992; Wilkinson and Carlen 1982), and neuropsychology (Ellis 1990).

The hypothesis evolved from early observations of structural brain changes in alcoholics. Courville (1966) characterized the post mortem appearance of brains of alcoholics as shriveled and reduced in size compared with brains of age-equivalent peers. Courville likened this appearance to the shrinkage associated with normal chronological aging. Other researchers have reported similar findings by using imaging techniques. Wilkinson and Carlen (1982), who compared CT brain scans of alcoholics ranging in age from their 20s to their 70s with scans of patients having medical conditions unrelated to alcoholism, found similar degrees of shrinkage in the brains of alcoholics and chronologically older nonalcoholics.

Alternate hypotheses have been proposed to explain the mechanisms of premature aging. According to one view, aging is accelerated at whatever age problem drinking commences. This is known as the accelerated aging hypothesis, which predicts that young alcoholics will become "old before their time," that cognitive deficits observed reflect additive effects of alcohol and aging, and that neuropsychological and brain changes in alcoholics should mimic those found in chronologically older nonalcoholics. According to a second view, vulnerability to alcohol-related brain damage is hastened only in people who are middle aged or older; that is, those in whom the normal manifestations of aging already have begun (see, for example, Oscar-Berman et al. 1993). This increased vulnerability hypothesis suggests that the brains of older alcoholics are more susceptible to the consequences of alcohol abuse. Thus, older alcoholics will demonstrate cognitive deficits that exceed the separate effects of aging and alcohol abuse, and they will suffer more age-related symptoms and impairments than will age-matched nonalcoholic peers and younger alcoholics with similar drinking histories.

Recent CT scan studies support the view that aging increases one's vulnerability to alcoholism-related brain damage; these studies showed a greater degree of brain tissue loss in older alcoholics than would be expected with aging alone (Kato et al. 1991; Pfefferbaum et al. 1988). Corroborating evidence comes from several laboratories that used MRI techniques (Hayakawa et al. 1992; Pfefferbaum et al. 1992) and electrophysiologic techniques (Cadaveira et al. 1992). In addition, it is worth noting that older alcoholics have an increased risk of unintended injuries, side effects, and overt toxicity related to alcohol that may be a consequence of concomitant medical problems and a decreased ability to metabolize alcohol. Taken together, most available evidence supports a link between alcoholism and premature aging and favors the increased vulnerability hypothesis.

However, studies using neuropsychological testing have yielded little evidence to support either premature aging hypothesis. Results from a few studies favor an age-related increase in vulnerability to alcohol-related cognitive decline (see Evert and Oscar-Berman 1995 for a review). For example, Ellis (1990) found that alcoholics between 48 and 74 years of age performed significantly worse than younger alcoholics (between 25 and 47 years of age) and age-matched nonalcoholic control subjects on certain portions of IQ tests; this finding appears to support the increased vulnerability hypothesis. The same study found that on dichotic listening tasks of right hemisphere function, however, older alcoholics showed no deficits out of proportion to their age in conjunction with their history of prolonged alcoholism; these results support an accelerated aging mechanism rather than an increased vulnerability to alcohol's effects. Results from other studies of right hemisphere functional decline in relation to alcoholism and aging have not been sufficiently consistent to resolve issues of accelerated aging due to alcohol use (reviewed by Ellis and Oscar-Berman 1989).

Family History

Although brain abnormalities in alcoholics often result directly or indirectly from alcohol use, recent evidence suggests that some brain changes may precede or even predict the development of alcoholism. Researchers have found that nondrinking adolescent and adult children of alcoholics show deficits in neuropsychological functioning (see Porjesz and Begleiter 1993 for a review). Some evidence suggests that children of alcoholics have problems with behavioral control (Windle 1994), visuospatial ability (Garland et al. 1993; Schandler et al. 1992), organization of novel information (Peterson et al. 1992), and short-term memory (Peterson et al. 1992). In a study that compared nonalcoholic men with and without a family history of alcoholism, Peterson et al. (1992) administered cognitive tests that were sensitive to frontal and temporal lobe function (such as organization of novel information and memory function, respectively). Subjects were tested while sober and while intoxicated. Results showed that men with a family history of alcoholism performed poorly on tests of frontal lobe function while sober and that intoxication had a detrimental effect on temporal lobe functions regardless of a family history of alcoholism.

> *Repeated withdrawal episodes may lead to progressively more severe withdrawal symptoms.*

A recent review of the many studies describing abnormal brain electrical activity in nondrinking sons of alcoholics has validated family history as an important contributing factor in the expression of these patterns (Polich et al. 1994). One such abnormality has been characterized as a reduced amplitude in an electrical component of the ERP known as the P300 (or P3). Because abstinent alcoholics display similar P3 abnormalities, researchers have viewed these brain waves as a potential phenotypic marker for alcoholism.

Following this line of reasoning, Berman et al. (1993) measured ERPs in young boys to determine whether ERPs might predict adolescent substance use. They found that a combination of reduced amplitude and prolonged latency in P3 significantly predicted adolescent substance abuse, including alcohol abuse. Another study has found that P3 amplitudes in children at high risk for developing alcoholism (those with first- or second-degree relatives who were alcoholic) are depressed relative to P3 amplitudes of low-risk children (those with no first- or second-degree relatives who were alcoholic) (Steinhauer and Hill 1993).

Withdrawal

Intoxicating concentrations of alcohol can nonspecifically suppress central nervous system activities, enhancing normal inhibitory processes and suppressing normal excitatory processes (Hoffman et al. 1989; Lovinger et al. 1989; Sudzak et al. 1986). However, alcohol withdrawal produces the opposite effect: Excitatory processes are enhanced and inhibitory processes are reduced (Morrow et al. 1988). This hyperexcited state involves alterations in neurotransmitter-controlled activities and elevated levels of adrenal hormones, including *cortisol* and norepinephrine (Adinoff et al. 1988). These alterations are associated with such symptoms as tremulousness, seizures, profuse sweating, and anxiety and also may contribute to neuronal damage.

Both cortisol and norepinephrine may be toxic to nerve cells (Linnoila et al. 1987). In particular, cortisol appears to damage neurons of the hippocampus (Sapolsky et al. 1986). Multiple episodes of withdrawal may mean multiple insults to the hippocampus, with corresponding changes in limbic system function. The neurotoxic effects of cortisol also may interact with effects of alcohol-associated thiamine deficiency or with neurotoxic effects of alcohol, thereby contributing to cognitive deficits observed with chronic alcohol dependence (Adinoff et al. 1991).

An alternate route of withdrawal-associated brain damage is through receptors for glutamate, the primary excitatory neurotransmitter in the brain. Chronic alcohol ingestion in laboratory rats increases the number of one type of glutamate receptor in the brain, an increase that is associated with enhanced susceptibility to alcohol withdrawal seizures (Hoffman 1995). Increased numbers of receptors may render these cells more susceptible to glutamate "excitotoxicity"—cell death resulting from excessive glutamate stimulation (Hoffman 1995). Repeated withdrawal episodes also may lead to progressively more severe withdrawal symptoms. This phenomenon has been demonstrated most clearly in laboratory animals. With repeated withdrawals, the animals show increasingly more intense brain electrical activity as well as alterations in glucose consumption in limbic system and cortical structures (Clemmesen et al. 1988; Poldrugo and Snead 1984). Some researchers have suggested that after a certain number of withdrawal episodes, the limbic system becomes increasingly more sensitive to the excitatory effects of additional withdrawal episodes. Over time, the consequences of repeated withdrawal episodes may include symptoms that occur spontaneously (Adinoff et al. 1995). Current research is focused on determining the mechanisms that produce withdrawal to identify pharmacotherapeutic agents that can prevent withdrawal-associated symptoms and neuronal damage (Adinoff et al. 1995; Hoffman 1995).

Recovery and Treatment

Studies suggest that alcoholics who remain abstinent for at least 4 weeks may experience a slow recovery of neuropsychological and cognitive functions, and certain brain scan imaging parameters (CT, MRI, and glucose metabolism) have been shown to improve with prolonged abstinence (Mann et al. 1993; Volkow et al. 1994). However, some alcoholics show persistent neuropsychological impairment with abstinence, including deficits on specific tasks of cognitive function. Numerous pharmacological treatments have been attempted to improve cognitive functioning in impaired alcoholics and have had varying effects (Martin and Nimmerrichter 1993).

Results from studies of cognitive recovery and treatments to improve neurocognition show no consistent trends, partly because researchers have yet to establish criteria defining complete recovery or the time period needed for recovery. In most studies of recovery, length of abstinence is about 4 weeks. Because recovery may continue over a much longer period, these studies may overestimate the permanence of neuropsychological deficits. One recent study has examined cognitive recovery in alcoholics at 3 to 4 months after treatment for alcoholism (Drake et al. 1995). Alcoholics were grouped according to family history of alcoholism and according to whether they had resumed drinking after treatment. Among alcoholics who had resumed drinking, those with a family history of alcoholism showed poorer performance on cognitive tests than did those with no history of alcoholism. This finding suggests that the former group may be more vulnerable to detrimental neuropsychological effects of continued alcohol consumption. However, abstainers showed significant improvement regardless of family history of alcoholism. Continued studies in this area, with establishment of consistent criteria for studying recovery, should aid in understanding the recovery process and in devising treatments for improving cognitive function in impaired alcoholics.

Alcohol and the Endocrine System

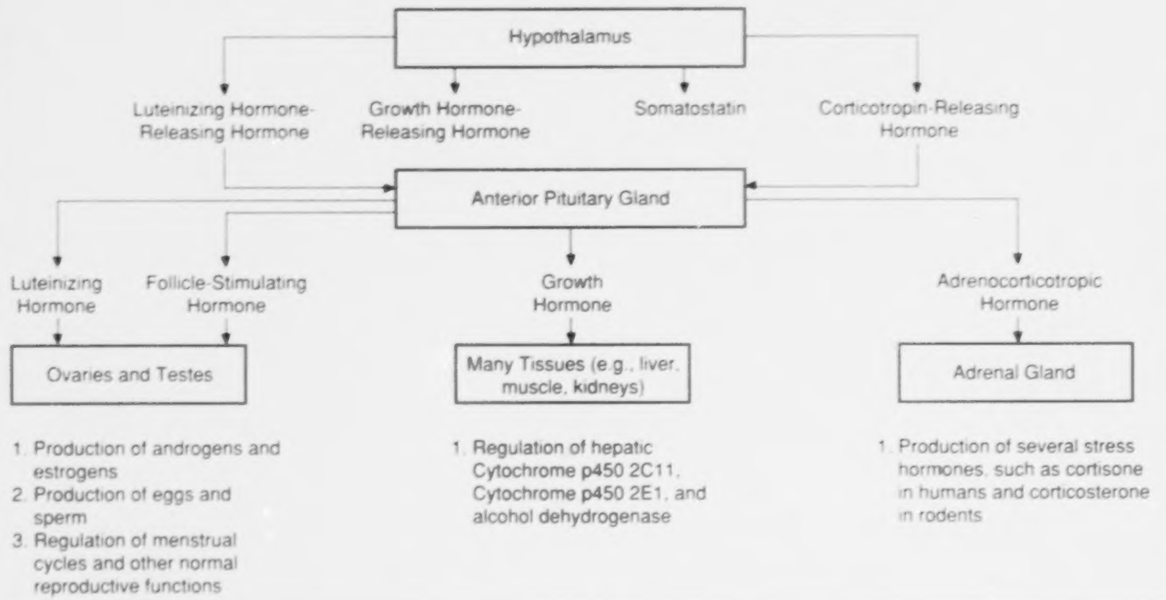
Hormones are critical for the control and maintenance of heart rate, blood pressure, body temperature, total body water, electrolyte concentrations, metabolism, growth, reproduction, and adaptation to stress. Alcohol may interfere with endocrine regulation of many of these activities.

Hormonal cascades involved in growth, reproduction, and stress response are depicted in figure 5. All three cascades operate under the control of the central nervous system through the actions of the *hypothalamus*, which interprets and translates signals from the brain by secreting *releasing hormones*. These releasing hormones travel via portal blood vessels to the anterior portion of the *pituitary gland*, which is located in a bony encasement of the skull immediately beneath the brain. Here, the releasing hormones stimulate secretion of pituitary hormones, which in turn regulate cellular activities in target organs and tissues.

Each hypothalamic releasing hormone initiates a different hormonal cascade. In one cascade, hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin act as stimulatory and inhibitory influences, respectively, that control pituitary secretion of growth hormone (GH). The result is a pulsatile, or episodic, pattern of GH secretion, and both the concentration and the pattern of GH release are important in GH-mediated processes. Interestingly, GH release patterns are sexually dimorphic, meaning that episodic release patterns in males differ from those in females. GH stimulates growth of hard and soft tissues in children and maintains the size of body parts once maturity is reached. GH also influences metabolic processes by directly promoting cell *proliferation* and *differentiation* and inducing production of other growth stimulators known as *somatomedins* (such as insulin-like growth factors, or IGFs). Somatomedins are synthesized primarily in the liver and are secreted into the circulation to affect cell growth and development in target tissues throughout the body, including tissues of the central nervous system (Baserga and Rubin 1993).

Luteinizing hormone-releasing hormone (LHRH) triggers a second cascade by stimulating pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Target tissues of LH and FSH include the ovaries and testes, where they induce secretion of *androgens* (such as *testosterone*) and *estrogens* (such as estrone and *estradiol*). These *gonadal steroids* are essential to normal reproductive functions, including development of reproductive organs, *spermatogenesis*, and ovulation. Importantly, gonadal steroids also control GH release, and GH participates in gonadal steroid control via regulation of steroid-metabolizing enzymes (Zachmann 1992).

Figure 5. Endocrine cascades and their roles in regulating body functions.


Hypothalamus
Luteinizing Hormone-Releasing Hormone
Growth Hormone-Releasing Hormone
Somatostatin
Corticotropin-Releasing Hormone
Anterior Pituitary Gland
Luteinizing Hormone
Follicle-Stimulating Hormone
Growth Hormone
Adrenocorticotropic Hormone
Ovaries and Testes
Many Tissues (e.g., liver, muscle, kidneys)
Adrenal Gland
1. Production of androgens and estrogens
2. Production of eggs and sperm
3. Regulation of menstrual cycles and other normal reproductive functions
1. Regulation of hepatic Cytochrome p450 2C11, Cytochrome p450 2E1, and alcohol dehydrogenase
1. Production of several stress hormones, such as cortisone in humans and corticosterone in rodents

A third hormonal cascade controls adaptive responses to stress through hypothalamic secretion of corticotropin-releasing hormone (CRH). CRH stimulates pituitary release of adrenocorticotropic hormone (ACTH), which in turn controls *corticosteroid* production by the *adrenal glands*. The hypothalamic-pituitary-adrenal hormonal cascade plays a primary role in maintaining *homeostasis* after a stressful stimulus. This response also has essential links with the immune system in that steroid hormones released during stress can alter immune functions; conversely, immune activation (for example, in reaction to an infectious agent) can result in the release of interleukin-1, a cytokine that is a potent stimulator of CRH release (Eskay et al. 1993).

Observed influences of alcohol in these endocrine cascades vary depending on whether alcohol exposure is acute or chronic, and the conditions of exposure must be considered in interpreting results. Studies of acute alcohol exposure, which are concerned with effects observed within minutes to hours of limited alcohol exposure, typically are easier to perform, control, and interpret than are studies of chronic alcohol exposure. In humans, studies of chronic alcohol consumption, which typically are clinical studies of alcoholics, are subject to complicating variables such as liver disease and nutritional deprivation; even in animal studies of chronic alcohol exposure, nutritional and stress factors may affect experimental results.

Growth Hormone

Adverse effects on GH-mediated functions may result when agents such as alcohol alter concentrations of GH (causing increased or decreased circulating levels of the hormone) or cause changes in its pulsatile secretion patterns. In laboratory animals, a single injection of alcohol reduces blood levels of GH; these levels normalize within 6 hours of alcohol exposure (Emanuele et al. 1992; Tentler et al. 1993). This alcohol-associated reduction may result from a decrease in the accumulation of GHRH-stimulated *cyclic adenosine monophosphate* (cAMP) in anterior pituitary cells. cAMP is an intracellular signaling molecule critical to a variety of cell functions, including GH release (Soszynski and Frohman 1992*b*; Tentler et al. 1993).

Laboratory animals chronically exposed to alcohol have depressed plasma concentrations of GH and IGF-1. Hypothalamic levels of GHRH mRNA also are reduced in these animals, whereas levels of hypothalamic somatostatin mRNA and pituitary GH mRNA are unchanged (Soszynski and Frohman 1992*a*). These results suggest that alcohol acts at the level of the hypothalamus to inhibit GH secretion. Because this pattern of hormonal events closely resembles that observed in animal studies of food deprivation (Bruno et al. 1990), effects attributed to chronic alcohol exposure may result from alterations in nutritional intake known to occur in many experimental models of chronic alcohol use (Smith et al. 1992*c*). Using a diet delivery system to control for such nutritional variables, Badger et al. (1993*b*) confirmed the findings of Soszynski and Frohman (1992*a*) and also showed that chronic alcohol consumption alters the episodic release pattern of GH in male rats to resemble that in female rats. Because sexual dimorphism patterns of GH secretion in rats are similar to those in humans, these studies suggest that human alcoholics may have similar alterations in GH secretion patterns. Furthermore, in view of the intimate interregulatory associations between GH and gonadal steroids, alcohol-related changes in patterns of GH release may contribute to alterations in reproductive functions observed in both laboratory animals and chronic alcoholics (see later discussion).

Alcohol also impairs activities of IGF-1 and related growth factors. In vitro experiments have shown that alcohol inhibition of IGF-1-stimulated cell proliferation is associated with reduced IGF-1 receptor *autophosphorylation*, which is an intracellular reaction necessary for IGF-1-dependent growth (Resnicoff et al. 1993). Other researchers have shown that in rats prenatally exposed to alcohol, IGF-1 and IGF-2 gene expression was reduced as were circulating levels of these growth factors. Furthermore, the animals had increased levels of circulating IGF-binding proteins, which are specialized proteins that may control bioavailability and activities of IGFs (Singh et al. 1994).

In addition to its effects on GH-mediated growth processes, alcohol may affect GH-regulated metabolic processes. GH controls gene expression of several liver cytochrome enzymes, including CYP2C11 and CYP2E1. A recent study has shown that chronic alcohol ingestion reduces levels of CYP2C11, an enzyme found in male rat liver cells that functions in gonadal steroid metabolism. This effect was attributed to alcohol-induced alterations in episodic patterns of GH release (Badger et al. 1993*b*). In contrast, chronic alcohol exposure stimulates production of CYP2E1 by increasing levels of CYP2E1 mRNA (Badger et al. 1993*a*; Ronis et al. 1993). That GH may regulate CYP2E1 has been suggested in studies showing that removal of the pituitary gland in laboratory animals (to eliminate GH) increases hepatic levels of this enzyme. CYP2E1 levels can then be normalized by GH replacement (Hong et al. 1990; Williams and Simonet 1988; Yamazoe et al. 1989). Current research is focused on determining the relationship between alcohol-related GH disturbances and alcohol-induced elevations of CYP2E1. In human populations, polymorphisms in the gene encoding CYP2E1 have been associated with cirrhosis (Maezawa et al. 1994).

GH also regulates expression of the gene for ADH, an enzyme with a primary role in the breakdown and elimination of alcohol from the body (Potter et al. 1993). Thus, through its effects on GH, alcohol may indirectly control functions of enzymes critical to metabolism of steroid hormones and alcohol.

Reproductive Hormones

Alcohol abuse has been associated with sexual dysfunction in men and women (see Becker 1993, Gavaler 1991, Wright et al. 1991, and Zakhari 1993 for reviews). Hormonal changes have been implicated in the diminished libido, impotence, testicular atrophy, decreased fertility, and *gynecomastia* associated with alcohol abuse in men. In women, the frequency of menstrual disturbances, spontaneous abortions, and miscarriages increases with the level of drinking, and alcohol abuse has adverse effects on fertility and sexual function (Mello et al. 1993).

Men who have a long-term history of alcohol abuse may exhibit a host of hormonal changes, including decreases in circulating levels of male sex steroids, such as testosterone and 5-alpha-dihydrotestosterone; increases in female sex steroids, such as estradiol and estrone, and in sex steroid-binding globulins (blood-transporting proteins that bind to and reduce the bioavailability of these hormones); and abnormalities in sex steroid metabolism (Wright et al. 1991; Zakhari 1993). Hormonal changes are observed with drinking even in nonalcoholic men. A recent study has shown that an acute, low-dose alcohol intake lowers serum testosterone in nonalcoholic men with no changes in LH; this finding suggests a direct effect of alcohol on the testes (Ida et al. 1992).

Significant advances have been made in understanding alcohol's effects on female reproductive function. Studies in laboratory animals have provided clues to the anatomical sites of alcohol-associated menstrual disturbances. For example, female sex hormone patterns have been studied in monkeys whose ovaries were removed (to simplify the complex feedback relationships that control reproductive hormone secretion). In these *ovariectomized* animals, administration of estradiol benzoate (a stable *ester* of estradiol) stimulates a surge of pituitary LH secretion; this effect is thought to be associated with increased LHRH release from the hypothalamus (Asch et al. 1983; Norman et al. 1986).

Glossary

Adrenal glands—Small glands located at the apex of each kidney that secrete *corticosteroids* and other hormones that help maintain *homeostasis.*

Androgen—Any of a group of *steroid* sex hormones produced in the testes that control masculinization and the function of male sex organs. Androgens are known as male sex hormones, but they are also produced by the ovaries and control sexual and other body functions in women.

Autophosphorylation—A chemical process by which a protein phosphorylates itself. Phosphorylation involves the formation of a phosphate-containing derivative, usually by an enzymatic process.

Corticosteroid—Any of a group of *steroid* hormones formed by the adrenal cortex, the outer layer of the *adrenal gland.*

Cyclic adenosine monophosphate (cAMP)—A molecule that serves as a signal to mediate intracellular changes in response to many neurotransmitters and hormones.

Differentiation—A developmental process by which cells become increasingly specialized, involving the acquisition of new characteristics and functions.

Ester—A compound formed by removal of water from an acid and an alcohol.

Estradiol—The most potent naturally occurring mammalian *estrogen.*

Estrogen—Any of a group of *steroid* sex hormones produced primarily by the ovaries that regulate female reproductive development. Estrogens are known primarily as female hormones but have a variety of functions in both sexes.

Glucocorticoid—Any of a group of *steroids* produced by the *adrenal glands* that regulate metabolism of carbohydrates, lipids, and proteins and are produced in response to stress. Glucocorticoids include cortisol and corticosterone.

Gonadal—Pertaining to sperm- or ovum-producing structures; that is, the ovary or testis.

Gynecomastia—Excessive growth of the male mammary glands.

Homeostasis—The body's capacity to maintain normal, internal stability by coordinated responses of organ systems that automatically compensate for environmental changes.

Hypothalamus—The lower portion of the diencephalon (a structure located in the posterior part of the forebrain) that interprets and translates signals from the brain by secreting hormones, including *releasing hormones.* The hypothalamus controls and integrates many nervous and endocrine system functions.

***N*-methyl-DL-aspartic acid**—A neurotransmitter that excites neurons.

Norepinephrine—A catecholamine neurotransmitter released primarily in response to low blood pressure or stress.

Ovariectomize—To surgically remove the ovaries.

Pituitary gland—A gland found in the base of the brain, connected by a stalk to the *hypothalamus.* It consists of an anterior portion, which secretes many hormones, and a posterior portion, which stores and secretes neurohormones.

Proliferation—Cell division and multiplication.

Releasing hormone—Hormone secreted by one structure, such as the *hypothalamus,* that affects the release of a hormone or hormones in another structure, such as the *pituitary gland.*

Somatomedin—Any of several peptides that are formed in the liver or other tissues and are found in the blood, often complexed with binding proteins that control their function or availability. Somatomedins stimulate cellular growth and replication.

Spermatogenesis—The process of formation of mature sperm.

Steroid—A large family of fat-soluble substances that includes many hormones and vitamins. Examples of steroids include the male and female sex hormones *testosterone* and *estrogen.*

Testosterone—The principal male sex hormone, produced primarily in the testes.

Mello et al. (1992) have demonstrated that acute alcohol exposure attenuates the pituitary release of estradiol benzoate in ovariectomized monkeys. On the basis of these and other published data, these researchers have suggested that alcohol acts at the hypothalamus to impair LHRH release and that similar mechanisms may contribute to the alcohol-associated menstrual cycle disruption observed in women.

Two recent clinical studies have documented a long-suspected relationship between alcohol consumption in women and circulating estrogen levels. The first study has shown that women with normal menstrual cycles who consumed alcohol equivalent to two drinks per day had increased levels of estrogens in plasma and urine (Reichman et al. 1993). The second, similar study has shown increased serum estradiol levels in postmenopausal women who consumed five drinks per week (Gavaler and Van Thiel 1992). A third study of women approaching menopause found no relationship between alcohol intake and serum estrogen levels (London et al. 1991). Thus, although available data generally support a link between alcohol and estrogen, resolution will require further investigation as will determination of the sites of action and mechanisms involved in alcohol's effects.

The impact of alcohol on estrogen levels may be related to an observed association between alcohol consumption and increased risk of breast cancer in women. However, data supporting this link between alcohol and breast cancer are controversial (Rosenberg et al. 1993; Schatzkin and Longnecker 1994). One compelling report has demonstrated that "drinkers of 3 or more glasses of alcoholic beverages per day appear to be at genuinely elevated risk for breast cancer" (Katsouyanni et al. 1994, p. 360). Although increased levels of estrogens may play a role in increasing risk of breast cancer (Henderson et al. 1993), the mechanisms involved and consistent data supporting such an effect are lacking (see Key and Pike 1988 for a review). Further investigation will be required to identify potential associations between alcohol, increased estrogen levels, and breast cancer. From a broader perspective, clarification of alcohol's effects on estrogen levels will be important in view of studies that show that estrogen and moderate drinking each may have protective effects in preventing postmenopausal cardiovascular disease (Gavaler et al. 1991) and studies that show estrogen replacement can deter progression of osteoporosis (Breslau 1994). Thus, potentially beneficial effects of alcohol consumption in preventing cardiovascular disease and osteoporosis must be weighed against the possibility of increased risk for breast cancer and other alcohol-associated endocrine-metabolic disorders.

Alcohol also adversely affects development of the reproductive system in experimental animals. Chronic alcohol exposure in prepubertal rats has been shown to delay onset of puberty and to reduce hypothalamic secretion of LHRH (Dees and Skelley 1990; Dees et al. 1990). Exposure of hypothalamic tissue from prepubertal rats to alcohol in vitro impaired induction of LHRH secretion by N-*methyl*-DL-*aspartic acid* and *norepinephrine*, which are known chemical stimulators of LHRH release (Hiney and Dees 1991; Nyberg et al. 1993). Because increases in LHRH release are thought to be a primary factor in triggering puberty, these findings may explain adverse effects of alcohol on pubertal development. They also suggest a hypothalamic site of alcohol action in regulating reproductive endocrinology during development.

A highly sensitive method known as reverse-transcriptase polymerase chain reaction (RT-PCR) has been used to examine effects of alcohol on regulation of genes encoding key hypothalamic and pituitary reproductive hormones (Kelley et al. 1993). Preliminary studies using these techniques have shown differential effects depending on whether alcohol exposure is acute or chronic. For example, in male rats, levels of pituitary mRNA encoding beta-LH (a subunit of LH) decreased with acute alcohol consumption but increased with chronic alcohol consumption (Emanuele et al. 1995). Continued studies in this area should help to discern alcohol's impact on endocrine function at the level of gene expression.

Paternal Exposure to Alcohol

That chronic alcohol consumption affects male and female reproductive functions is well established as are the detrimental effects of maternal alcohol consumption on the fetus. An interesting new area of alcohol research examines whether paternal alcohol consumption also causes harm to offspring. In laboratory animals, paternal alcohol consumption has been shown to alter a variety of behaviors in offspring (Abel and Bilitzke 1990; Abel and Lee 1988; Wozniak et al. 1991). Related studies have shown that male rats that were chronically exposed to alcohol, slowly withdrawn from alcohol, and then mated with alcohol-naive females produced fewer offspring. In addition, as adults, these offspring had lower serum testosterone levels and lower weights of secondary sex organs than control offspring had (Cicero et al. 1990). Recent evidence suggests that a single intoxicating dose of alcohol in healthy alcohol-naive rats can reduce fertility (Cicero et al. 1994). In these studies, male rats were injected with alcohol and then mated after clearance of alcohol from the blood. The outcome was a reduction in the frequency of pregnancy and litter size and an increase in mortality of offspring. Thus, chronic or acute paternal alcohol consumption may impact behavior, fertility, and reproductive development of offspring.

Stress Response

Associations between long-term alcohol abuse and abnormalities in stress hormone cascades are well established. Investigators have begun to examine effects of acute alcohol consumption in altering endocrine stress responses and have come up with mixed results. Ida et al. (1992) have reported that acute alcohol exposure in nonalcoholic males produces no change in the levels in ACTH or cortisol despite decreasing serum testosterone (see earlier discussion). Other investigators have shown that mild intoxication in nonalcoholic men blunts CRH-stimulated ACTH and cortisol levels, which suggests that alcohol may impair normal pituitary-adrenal responses to physiologic stressors (Waltman et al. 1993).

Related studies have shown that laboratory animals subjected to stress may increase their alcohol intake (Pohorecky 1981). That stress is also accompanied by increased secretion of pituitary and adrenal hormones suggests that these hormones may influence drinking behavior. Observations by Fahlke et al. (1994) support this idea. They found that adrenalectomized rats decrease their alcohol consumption and that corticosterone replacement in these animals restores alcohol intake to preoperative levels. Thus, corticosteroids may participate in modulating alcohol intake.

Alcohol withdrawal syndrome, a common reaction of alcohol-dependent people to abrupt cessation of drinking, has been associated with a marked activation of the stress hormone cascade (Adinoff et al. 1991). The investigators observed significant elevations in cortisol during alcohol withdrawal, particularly during the initial, acute phase of this response. Because excessive exposure to cortisol and other *glucocorticoids* may have neurotoxic effects, glucocorticoid elevations may explain some of the behavioral and neurological changes associated with withdrawal. Other researchers have compared mouse strains that differ in severity of their withdrawal responses to show that the magnitude of stress responses (measured in terms of serum ACTH and corticosterone) directly correlates with the degree of severity of withdrawal symptoms (Roberts et al. 1992).

Stress Responses and Interleukins

IL-1beta, one of numerous cytokines that regulate immune responses, also participates in stress responses. IL-1beta stimulates hypothalamic cells to release CRH, which sets off the cascade of pituitary ACTH and adrenal corticosteroid release. Administration of alcohol to male rats and ovariectomized female rats has been shown to reduce IL-1beta-induced ACTH secretion (Lee and Rivier 1993, 1995). Further study has shown that in female rats chronically exposed to alcohol, sex steroids of ovarian origin can further blunt the inhibitory effect of alcohol on IL-1beta-induced ACTH secretion. These findings suggest that alcohol in combination with reproductive hormones can influence endocrine regulation of stress responses and that alcohol may alter normal interactions between the immune system and neuroendocrine system (Lee and Rivier 1994*a,b*).

> *Alcohol in combination with reproductive hormones can influence endocrine regulation of stress responses.*

Alcohol and the Immune System

In healthy individuals, the complex network of lymphoid cells and regulatory cytokines that compose the immune system (see sidebar) efficiently detects and eliminates bacteria, viruses, and cancer cells. Alcohol exposure, particularly chronic or abusive alcohol exposure, may adversely alter lymphoid cell and cytokine activities to yield a chaotic and poorly coordinated immune defense. The result may be a generalized suppression of resistance to infectious agents and other pathogens. In addition, with long-term alcohol abuse, dysregulation of the immune system combined with alcohol-associated damage to the liver and other tissues may precipitate autoimmune lymphoid cell reactions that further injure these tissues.

The Developing Immune System

Exposure to alcohol disrupts the normal development and maturation of the immune system, as is suggested by the increased frequency of infections observed in children with fetal alcohol syndrome, especially during the first 2 years of life (Johnson et al. 1981). Studies in laboratory animals have revealed some of the deficits precipitated by prenatal alcohol exposure. For example, offspring of rats and mice exposed to alcohol during pregnancy have reduced numbers of thymocytes (Ewald and Walden 1988; Norman et al. 1991; Weinberg and Jerrells 1991); in rats, the remaining thymocytes show enhanced proliferation in the presence of *Concanavalin A* (Con A), a substance that induces cell division and that is used to test T-lymphocyte proliferative responses (Wong et al. 1992). In contrast, prenatal exposure to alcohol inhibits proliferation of IL-2- or Con A-stimulated T lymphocytes (Weinberg and Jerrells 1991). Differences between thymocyte and T-lymphocyte responses may reflect alcohol-induced alterations in T-lymphocyte development within the thymus (Wong et al. 1992).

Alcohol exposure can also alter immune functions during early postnatal life, when the immune system is still developing. Exposure of laboratory mice to alcohol in maternal milk produces long-term deficits in in vivo cellular immune responses (Gottesfeld and LeGrue 1990). Rats exposed to alcohol prenatally and during lactation or during lactation only have reduced numbers of splenic B lymphocytes and T lymphocytes (Giberson and Blakley 1994). Female rats fed alcohol during pregnancy and lactation have reduced antibody responses to a parasite antigen and demonstrate other immune deficits (Steven et al. 1990). Because at least part of early resistance to infection results from the transfer of maternal antibodies and lymphoid cells in amniotic fluid or milk, it follows that these effects on maternal immune competence may impact that of the offspring (Steven et al. 1990).

Lymphoid Cell Populations

Alcohol alters lymphoid cell responses in different ways depending on the type of lymphoid cell or immune function studied and whether alcohol exposure is acute or chronic.

Animals chronically exposed to alcohol have reduced numbers of lymphoid cells in the thymus, bone marrow, spleen, and *mesenteric* lymph nodes; the immature populations of the thymus are the most severely affected (Kruger and Jerrells 1994; Saad and Jerrells 1991). In vitro and in vivo studies suggest that alcohol may deplete thymocytes by *apoptosis,* a process of programmed cell death (Ewald and Shao 1993; Han et al. 1993). In vivo, apoptosis was observed after a single large dose of alcohol and appears to result in part from the actions of glucocorticoids induced in response to stress (Han et al. 1993). Apoptosis normally is part of a selective process that establishes the antigen-recognizing capability of thymocytes as they develop into T lymphocytes. Alcohol-induced apoptosis may involve indiscriminate thymocyte destruction and may thereby deplete T-lymphocyte populations crucial for resistance to particular pathogens.

Alcohol may deplete thymocytes by apoptosis, a process of programmed cell death.

Chronic alcohol ingestion in mice depletes immature B cells in the bone marrow; this effect is even more pronounced after alcohol withdrawal (Kruger and Jerrells 1994). In the spleen, total lymphocyte numbers decline: B-lymphocyte numbers are sharply reduced, whereas T-lymphocyte numbers are increased (Hsiung et al. 1994; Saad and Jerrells 1991). In mesenteric lymph nodes, numbers of both B lymphocytes and T lymphocytes are reduced; CD4 and CD8 T lymphocytes are the most significantly affected with continued alcohol consumption (Sibley 1995). Collectively, these studies indicate that alcohol disrupts normal maturation and trafficking of lymphocytes in central and peripheral lymphoid organs.

Alcohol ingestion also alters defensive activities of B lymphocytes, T lymphocytes, NK cells, and other lymphoid cells. Chronic alcohol consumption reduces T-lymphocyte proliferative responses (Jerrells 1989; Jerrells et al. 1990). Comparison of mice of different ages shows that this T-lymphocyte suppression is more pronounced in younger and older mice (Domiati-Saad and Jerrells 1993). That blood alcohol levels were also highest in younger and older mice suggests a dose-related effect of alcohol (Jerrells 1989). Other researchers have confirmed that alcohol-fed mice have impaired cell-mediated immune responses, as has been determined by in vivo *hypersensitivity* tests and by measurements of antigen-stimulated lymphocyte proliferation in vitro (Waltenbaugh et al. 1994). In contrast, these researchers found that alcohol enhances antigen-specific humoral responses (i.e., antibody production) in these animals (Waltenbaugh et al. 1994), possibly as a result of alterations in cross-regulatory activities of CD4 lymphocyte subpopulations that control antibody production (Hsiung et al. 1994; Waltenbaugh and Hsiung 1994).

In the intestinal *epithelium* of alcohol-fed rats, lymphocyte numbers are generally depleted, but the numbers of B lymphocytes secreting *immunoglobulin* A (IgA, a class of antibody important in intestinal immune responses) are proportionately increased. These animals also had significant elevations of serum IgA in association with the development of IgA-related kidney pathology, which is a frequent complication in alcoholics with liver disease (Amore et al. 1994; Smith et al. 1992*b*). In mice, long-term alcohol consumption suppresses killing of tumor cells by splenic and blood NK cells (Blank et al. 1992, 1993) and may explain the decreased resistance to tumor *metastasis* observed in alcohol-fed rats (Yirmiya et al. 1992). Alcohol-induced suppression of NK cell activity is reversible in vitro by treatment with IL-2 (Gallucci et al. 1994).

In humans, alcohol abuse is associated with a generalized immunosuppression and dysregulation of immune responses (Cook et al. 1991, 1994). A recent study has shown that alcoholic patients without liver disease have elevated numbers of circulating T lymphocytes and decreased numbers of B lymphocytes and NK cells in comparison with nonalcoholic control subjects (Cook et al. 1994). Elevated levels of activated CD8 T lymphocytes were observed in these patients; investigation of cell surface markers defining T-lymphocyte subpopulations revealed significant alterations, indicating a loss of regulatory function and a gain of cytotoxic potential. Such alterations may contribute to autoimmune liver damage (see later discussion) and may explain other immunologic abnormalities associated with chronic alcohol exposure

Glossary

Antigen—Any substance that is recognized by B *lymphocytes* or T lymphocytes and that stimulates these cells to mount an immune response.

Apoptosis—A process of programmed cell death; part of a selective process that establishes the *antigen*-recognizing capability of thymocytes as they develop into T *lymphocytes*.

Concanavalin A (Con A)—A plant lectin that stimulates proliferation of certain lymphoid cells and is used to study T-*lymphocyte* functions in vitro.

Epithelium—The covering or lining tissue of the body.

Hypersensitivity—A condition in which components of the immune system overreact or respond in an inappropriate manner, causing tissue damage.

Immunoglobulin—A protein produced in response to, and that interacts with, *antigen*. B *lymphocytes* produce immunoglobulins, also known as antibodies.

Interferon-gamma—One of a group of proteins known as interferons that increase the resistance of cells to viral infection. Interferons also act as cytokines and can enhance some immune responses.

Lymphocyte—A white blood cell that is able to specifically recognize and respond to an *antigen*. Lymphocytes include B lymphocytes and T lymphocytes.

Lymphoid organs—The organs in which *lymphocytes* develop and congregate. Those organs in which lymphoid cells develop, the bone marrow and thymus, are called central lymphoid organs; peripheral lymphoid organs include the spleen, lymph nodes, and tonsils.

Mesenteric—Pertaining to the membrane that supports or suspends the abdominal organs.

Metastasis—The spread of disease from one organ or part to another, due either to the spread of pathogenic microorganisms or to the movement of cells, such as cancer cells.

Neoantigen—A tumor cell protein or normal protein that is modified by a chemical reaction so that it is recognized as foreign by cells of the immune system.

Opportunistic—Pertaining to a microorganism that ordinarily does not cause disease but does so under certain circumstances, such as when the immune system is impaired as a result of disease or drug treatment.

Phagocyte—A white blood cell capable of ingesting foreign particles and microorganisms.

Pulmonary—Pertaining to the lungs.

Sensitization—Initial exposure to *antigen* that results in the development of an initial, specific immune response.

(Cook et al. 1994). Acute alcohol consumption does not appear to affect NK-cell activity in humans; however, NK-cell activity of human peripheral blood lymphoid cells is suppressed by alcohol treatment in vitro (Ochshorn-Adelson et al. 1994). Effects of long-term alcohol consumption on NK-cell activity in humans remains to be addressed.

Cytokine Production

Alcohol disrupts cytokine regulation of immune responses by altering cytokine release and expression or function of cytokine receptors found on the surfaces of lymphoid cells. Functional defects of T lymphocytes observed in alcohol-fed mice (discussed earlier) result at least in part because of an inability to respond to IL-2 rather than from impairment of IL-2 production. These findings indicate an alteration in IL-2 receptor function (Jerrells 1989; Jerrells et al. 1990). Exposure to alcohol interferes with production and regulatory activities of TNF-alpha, IL-6, and IL-1. These cytokines are produced by macrophages and other cells that play central roles in protective inflammatory responses to bacterial infections (Martinez et al. 1992). For example, alcohol treatment of mouse spleen cells and human peripheral blood cells suppresses TNF-alpha and *interferon* (IFN)-*gamma* production in response to endotoxin, which is a component of bacterial cell walls (Chen et al. 1993; Verma et al. 1993). In laboratory animals injected with endotoxin, acute but not chronic alcohol ingestion decreases serum and lung levels of TNF-alpha (D'Souza et al. 1989; Nelson et al. 1989*b,c*). Acute alcohol ingestion also interferes with binding of TNF-alpha to its receptors on neutrophils and inhibits expression of TNF-alpha receptors and IL-6 receptors on lung macrophages (Deaciuc et al. 1992; D'Souza et al. 1994). In mice, chronic alcohol ingestion suppresses spleen cell and thymocyte production of IL-1, IL-2, IL-6, IFN-gamma, and other cytokines, including IL-10, which regulates development and function of some CD4 T lymphocytes, and IL-4, which augments antibody production and T-lymphocyte proliferation (Nanji et al. 1994*e*, Wang et al. 1994*b*). Vitamin E supplementation restores IL-2, IL-6, and IL-10 responses in these animals; this observation suggests that nutritional factors may alleviate some of alcohol's suppressive properties (Wang et al. 1994*a*). In contrast to its effects on other cytokines, alcohol enhances production of TGF-beta by human blood macrophages (Szabo et al. 1992). Because TGF-beta inhibits T-lymphocyte and macrophage activities, these findings are consistent with the generally immunosuppressive effects of alcohol on the immune system (Szabo et al. 1992).

Resistance to Infection

The culmination of alcohol's effects on various elements of the immune system is a general suppression of host resistance to bacterial and viral diseases.

Bacterial Infections

The association between alcohol misuse and increased frequency and severity of bacterial infections, such as pneumonia and tuberculosis, is well documented (Roselle 1992). Many of the bacteria causing these infections are ***opportunistic***, meaning that they cause disease only in immunocompromised people. In mice, alcohol has been found to impair T-lymphocyte-mediated responses to *Listeria monocytogenes* (an opportunistic bacterium that causes ***pulmonary*** infections in humans), resulting in both increased susceptibility to infection and increased disease severity (Saad et al. 1993). In a rat model used to study mycobacterial infection, chronic alcohol consumption significantly impaired normal bacterial clearance activities of T lymphocytes and macrophages. The findings may explain the decreased resistance of alcoholics to mycobacterial infections such as tuberculosis and mycobacterial hepatitis (Mendenhall et al. 1990). Chronic alcohol consumption also inhibits production of toxic oxidants by lung macrophages. Because these oxidants are the primary means by which macrophages kill bacteria, these studies suggest that alcohol abuse may contribute to the establishment of pulmonary disease and may explain, in part, the association between alcoholism and increased susceptibility to bacterial pneumonia (Antony et al. 1993).

Advances in understanding alcohol's effects on cytokine production have stimulated research in therapeutic approaches to augment immune responses in infection-prone alcoholics. Recent studies show that antibacterial activities of granulocytes (a group of inflammatory lymphoid cells that include neutrophils) are markedly suppressed in intoxicated rats with bacterial pneumonia. Administration of granulocyte colony stimulatory factor, a cytokine that influences the maturation and release of granulocytes from bone marrow, overcomes this suppression and aids survival (Nelson et al. 1989*a*, 1991). These results suggest that this therapy may one day help to prevent and treat infections in alcohol-immunocompromised patients.

Alcohol may impair B-cell functions that would protect against HBV hepatitis.

Viral Hepatitis

Alcoholics have an increased risk for viral hepatitis, which is usually caused by hepatitis B virus (HBV) or hepatitis C virus (HCV), for reasons not fully understood and that may relate only in part to alcohol-associated immunosuppression. Studies have shown that higher percentages of patients with alcoholic liver damage have antibodies to HBV, HCV, or both than are found in the general population (Mendenhall et al. 1991; Nalpas et al. 1991; Zignego et al. 1994). In addition, the presence of antibodies to HCV correlates with accelerated onset or clinical severity of liver disease (Mendenhall et al. 1991, 1993; Nalpas et al. 1991).

In patients with chronic HCV infection, continued alcohol consumption suppresses cellular immunity and increases detectable virus in the blood; thus, alcohol use may enhance viral replication, depress immune functions that may help eliminate the virus, or both (Oshita et al. 1994). In addition, alcohol has been shown to interfere with protective antibody responses elicited with HBV vaccine, which suggests that alcohol impairs B-cell functions that would protect against HBV hepatitis (Nalpas et al. 1993).

Alcohol and AIDS

Despite the increased susceptibility to infections observed in alcoholics, the role of alcohol in infection with the human immunodeficiency virus (HIV) (McManus and Weatherburn 1994) or development of acquired immunodeficiency syndrome (AIDS) (Kaslow et al. 1989) has not been clearly delineated. (For a discussion of alcohol-associated risk-taking behaviors that may increase the likelihood of acquiring HIV infections, see Chapter 7, Effects of Alcohol on Behavior and Safety.) However, studies performed on lymphocytes from healthy subjects indicate that alcohol consumption compromises CD4 T-lymphocyte functions, suppresses Con A-stimulated IL-2 production, and enhances in vitro replication of HIV (Bagasra et al. 1989, 1993). In addition, because alcohol and AIDS both suppress the immune system, it is possible that alcohol use by HIV-infected individuals may exacerbate the severity of opportunistic infections that frequently occur with AIDS.

The Immune System

The immune system comprises an intricate array of specialized lymphoid cells that function to defend the body against infectious agents and other pathogenic substances. Lymphoid cells include B lymphocytes, T lymphocytes, thymocytes (immature T lymphocytes), natural killer (NK) cells, macrophages, and neutrophils, which develop in the bone marrow and thymus and travel in blood and lymph to peripheral lymphoid organs, such as the lymph nodes and spleen. Lymphoid cells eliminate pathogens by (1) nonspecific reactions, which form a first line of defense because they require no previous exposure to the invader, and (2) specific reactions, which involve sensitization and recognition of pathogen-associated proteins known as antigens.

Macrophages, neutrophils, and NK cells play critical roles in nonspecific immune responses. Macrophages, which are found in tissues and fluids throughout the body, are phagocytes that literally consume and degrade microbes and foreign substances and help keep organs such as the liver and lungs free from disease. Neutrophils also have phagocytic properties and are among the first cells to arrive at a site of infection or tissue injury. NK cells provide a crucial defense against virus-infected cells and certain types of spontaneously arising tumor cells. NK cells bind directly to and destroy foreign cells by mechanisms that are incompletely understood.

Specific immune reactions are carried out by B lymphocytes and T lymphocytes. B lymphocytes are bone marrow-derived cells responsible for antibody production. The presence of antigen stimulates these cells to proliferate and secrete antibodies into body fluids, or humors (thus, B-lymphocyte activities are often referred to as "humoral" immune responses). T lymphocytes develop from bone marrow-derived cells that migrate and mature in the thymus. Because T lymphocytes interact directly with virus-infected cells or cancerous cells, their activities are often referred to as "cellular" immune responses. T lymphocytes can be classified based on their respective expression of surface proteins designated CD4 and CD8 and by characteristic responses to antigenic stimulation. CD4 T lymphocytes, or helper T lymphocytes, react to antigen by secreting cytokines, which are substances that regulate immune reactions of T lymphocytes and other lymphoid cells. CD4 T lymphocytes may be further broken down into subpopulations that can enhance or inhibit activities of T lymphocytes and other lymphoid cells to achieve a balanced immune response. CD8 T lymphocytes become activated in response to antigens on virus-infected cells or transplanted cells and develop cytotoxic properties that destroy these cells. Normal T-lymphocyte responses require that antigen be present in association with multiple histocompatibility complex proteins. Presentation of antigen is performed by macrophages, B lymphocytes, and other specialized cells.

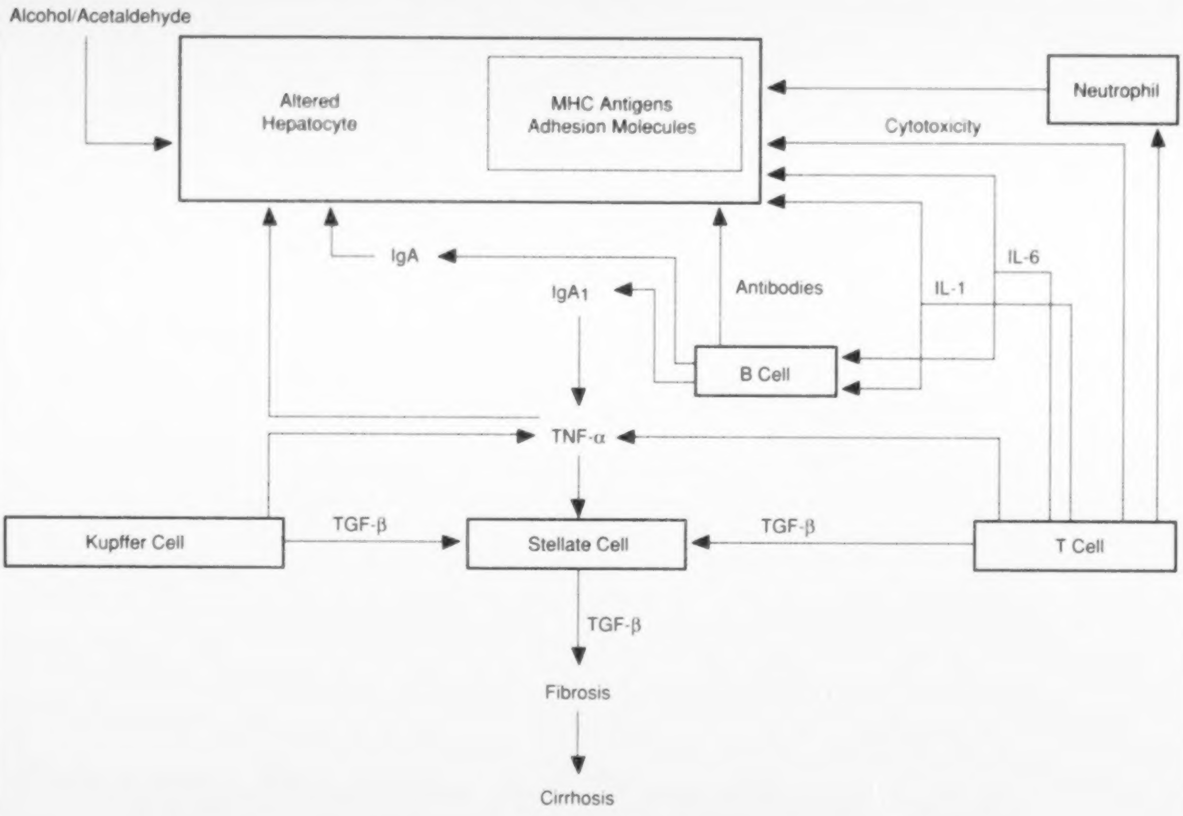
Cytokines orchestrate the responses and interactions of these various lymphoid cells. Cytokines are produced by T lymphocytes as well as other lymphoid and nonlymphoid cells and include interleukin (IL)-1 and tumor necrosis factor (typically macrophage products) as well as IL-2 and interferon-gamma (typically T-cell products). These substances exert their regulatory functions by interacting with specific receptors on lymphoid cell surfaces. ❑

Studies using mice with a viral infection similar to human AIDS (called murine AIDS, or MAIDS) have shown that suppressed B-lymphocyte and T-lymphocyte proliferation resulting from viral infection is further reduced by alcohol ingestion (Wang et al. 1993*a*; Wang and Watson 1994). These studies also showed that alcohol consumption alters production of cytokines normally stimulated by viral infection, which suggests a generalized dysregulation of normal immune responses that may exacerbate progression to MAIDS. In addition, alcohol impairs host resistance of mice with MAIDS to pneumonia caused by *Cryptosporidium* and *Streptococcus*, which are opportunistic pathogenic microorganisms that commonly infect AIDS patients (Alak et al. 1993; Shahbazian et al. 1992). Although such findings support a role for alcohol in aggravating the progression and complications of AIDS in humans, they should be interpreted with caution because of significant differences between the mouse model and the human disease (Cunningham et al. 1994).

Alcohol and Liver Immunopathology

Immunological abnormalities observed with long-term alcohol abuse in humans can include autoimmune processes that damage liver tissues. The processes behind this immunopathology are complex and incompletely understood. Some of the mechanisms thought to be

Figure 6. Immunological pathogenesis of alcohol-induced liver cirrhosis: proposed mechanisms.



MHC = Multiple histocompatibility complex
IgA = Immunoglobulin A
IL-6 = Interleukin-6
IL-1 = Interleukin-1
TNF = Tumor necrosis factor
TGF = Transforming growth factor

Source: Adapted from Paronetto 1993. Reprinted by permission of the publisher.

involved are summarized in figure 6 and are extensively reviewed by McClain et al. (1993) and Paronetto (1993).

Changes in the liver associated with alcohol misuse include the formation of altered liver cell proteins resulting from covalent bonding of acetaldehyde to form acetaldehyde adducts (Klassen et al. 1994). These adducts are thought to represent *neoantigens* (literally, "new antigens") that are perceived as foreign by lymphoid cells. As such, these neoantigens may stimulate antibody production (typically IgA), activate cytotoxic (CD8) T lymphocytes, and incite neutrophil inflammatory activity, thereby resulting in direct damage to liver cells. Hepatocytes from patients with alcoholic liver disease have increased expression of multiple histocompatibility complex proteins (Chedid et al. 1993*b*). Because these proteins are required for T-lymphocyte antigen recognition, their increased expression may render hepatocytes more susceptible to cytotoxic T-lymphocyte damage. CD4 T lymphocytes may be stimulated as well and may contribute cytokines that promote and sustain lymphoid-mediated destruction (Chedid et al. 1993*b*). Antibody accumulation along liver cell membranes triggers macrophage production of TNF-alpha, which may in turn activate collagen-producing stellate cells of the liver, thus resulting in formation of fibrous scars (Paronetto 1993). Blood levels of other cytokines, principally IL-1, IL-6, and TGF-beta, are elevated in patients with alcoholic liver disease, probably as a result of activation of macrophages or Kupffer cells (a type of macrophage endogenous to the liver) in liver tissues. IL-1 and IL-6 may help sustain lymphoid cell autoreactivity, and TNF-alpha and TGF-beta may contribute to stellate cell activation (Paronetto 1993).

In addition, both hepatocytes and lymphoid cells from people with alcoholic liver disease have been shown to have increased expression of adhesion molecules, which are proteins that assist in the recruitment of lymphoid cells to sites of inflammation and attachment of T lymphocytes to target cells (Adams et al. 1994; Chedid et al. 1993*a*). The combination of these and other destructive forces can lead to fibrotic and cirrhotic changes characteristic of alcoholic liver disease.

Summary

Excessive alcohol consumption may have widespread deleterious effects on all tissues and organs of the body. The result is a diverse array of medical consequences spanning neuropsychological and reproductive abnormalities and increased susceptibility to infection. Sometimes effects of alcohol on one organ system can impair another; for example, alcoholic liver disease may lead to metabolic and physiologic changes that alter neurological function. Alcohol abuse also contributes to heart and cardiovascular disease, although light drinking appears to have some benefits for cardiac health.

Alcohol abuse causes liver inflammation and progressive liver scarring (fibrosis or cirrhosis). Mechanisms that contribute to liver damage include endotoxin stimulation, cytokine release, and the formation of free radicals and acetaldehyde-protein adducts that may directly damage liver cells or incite inflammatory autoimmune reactions. Alcohol stimulates Kupffer cell production of oxygen radicals and cytokines that may contribute to inflammation and tissue injury. Alcoholic fibrosis is thought to be precipitated by acetaldehyde-induced collagen deposition by stellate cells. A promising approach to preventing fibrosis involves administration of polyunsaturated soybean lecithin, which may promote the breakdown of hepatic collagen.

Heavy alcohol consumption can interfere with the mechanical functions of the heart. Progressive functional changes and tissue damage may lead to cardiomyopathy and heart failure. Chronic alcohol consumption depresses heart muscle contractility, and toxic alcohol metabolites may damage heart muscle tissue. Excessive alcohol consumption also is associated with hypertension and an increased risk for CAD and stroke. However, light to moderate drinking appears to be beneficial in preventing CAD (perhaps by elevating blood levels of HDL or by inhibiting clotting processes that contribute to atherosclerosis and thrombosis).

Alcohol-associated neuropsychological disorders typically involve damage to the limbic system, the diencephalon, and the frontal cerebral cortex of the brain. Among the numerous and diverse neuropsychological consequences of chronic alcohol abuse are deficits in short-term memory, reduced visuospatial and other perceptual abilities, and emotional and personality changes. Currently, researchers are attempting to elucidate the connections between alcohol-associated alterations in brain structure and metabolism and alcohol-associated neuropsychological changes.

Numerous studies indicate that alcohol impairs endocrine functions. Notable among these effects is the alteration of GH secretion patterns observed with chronic alcohol exposure. Disruption of GH secretion, in turn, may cause a variety of metabolic and endocrine changes because GH controls the levels of other growth stimulators as well as alcohol- and steroid-metabolizing enzymes. Alcohol abuse may profoundly impair reproductive development and function in both men and women. Recent studies in women show that alcohol consumption may increase estrogen levels; this effect may be related to an observed association between alcohol consumption and increased risk for breast cancer. With alcohol withdrawal syndrome, marked elevations in glucocorticoid stress hormone are observed. Glucocorticoids in excess may be neurotoxic; thus, glucocorticoid elevations may explain in part the behavioral and neurological changes observed with withdrawal.

Alcohol consumption, particularly of a chronic or abusive nature, depresses immune system function by altering the distribution and function of lymphoid cells and by disrupting cytokine regulation of lymphoid cell activities. The result may be a poorly coordinated immune response and an increased susceptibility to bacterial and viral infections. Immunological abnormalities observed with long-term alcohol abuse in humans also include autoimmune processes that damage liver tissues.

Collectively, these findings represent significant advances in understanding the disease processes associated with excessive alcohol use. A better understanding of the mechanisms involved is a necessary step toward an important goal—the prevention or alleviation of the deleterious consequences of alcohol abuse.

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Chapter 6

Effects of Alcohol on Fetal and Postnatal Development

Introduction

Since fetal alcohol syndrome (FAS) was first identified independently in France (Lemoine et al. 1968) and in the United States (Jones et al. 1973), more than 2,000 scientific reports have been published about the harmful effects of alcohol on the fetus (Streissguth et al. 1991). These reports trace the evolution and document the advances of this research area, including the clinical recognition of alcohol-induced birth defects, the experimental establishment of alcohol as a physical and behavioral *teratogen*,[1] the development of animal models to explore mechanisms underlying fetal defects, and the pursuit of clinical studies to assess the specific relationships between prenatal alcohol exposure and fetal development. Findings from many of these reports have been reviewed in previous editions of the *Special Report to the U.S. Congress on Alcohol and Health*.

This chapter builds on the overview presented in the last Special Report by highlighting current knowledge about the effects of alcohol on pregnancy outcome. Because the literature in this area is vast, this review considers only a selection of current work, to provide a sense of the significant currents in the field. The first section examines recent progress made in clinical studies. Among the topics discussed are diagnosis and incidence of FAS, followup studies examining the long-term developmental problems associated with FAS, prospective longitudinal studies that consider the scope of maternal drinking practices and the spectrum of defects that can occur in offspring, differences among offspring in their vulnerability to FAS, and measures to prevent alcohol-induced birth defects. The second section describes animal studies. Recent findings on the general principles of alcohol teratogenesis, consequences of prenatal alcohol exposure in animals, potential risk factors for alcohol-related birth defects (ARBD), and mechanisms of alcohol teratogenesis are presented.

Diagnosis of Fetal Alcohol Syndrome

A key concern in research and clinical practice continues to be how best to characterize and identify FAS and other ARBD arising from prenatal alcohol exposure. Research has shown that in utero alcohol exposure can produce a spectrum of harmful effects, ranging from a characteristic pattern of gross morphological anomalies and mental impairment (including mental retardation) to more subtle cognitive and behavioral dysfunctions. FAS is the most severe birth defect produced by in utero alcohol exposure. The terms "fetal alcohol effects" (FAE) and "alcohol-related birth defects" are used to describe individuals who exhibit only some of the attributes of FAS and thus do not fulfill the diagnostic criteria for the syndrome (Clarren and Smith 1978; Sokol and Clarren 1989).

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[1] For a definition of *teratogen* and other terms in this chapter, see the glossary.

Diagnostic Criteria

The diagnostic criteria for FAS, which were initially standardized by the Fetal Alcohol Group of the Research Society on Alcoholism (Rosett 1980) and later modified by Sokol and Clarren (1989), are the following:

1. Prenatal or postnatal growth deficiency or both (weight or length or both below the 10th percentile when corrected for gestational age).
2. Central nervous system (CNS) disorders, including neurological abnormality, developmental delay, intellectual impairment, and structural abnormalities.
3. A distinctive pattern of facial anomalies, including short palpebral fissures (eye openings); a thin upper lip; an elongated, flattened midface; and an indistinct philtrum (the zone between the nose and the mouth).

Maternal alcohol use during pregnancy should be documented to confirm an FAS diagnosis (Aase 1994).

Despite consensus regarding these criteria, researchers and clinicians continue to experience considerable difficulty in diagnosing FAS, in large part because none of the characteristic abnormalities is specific to the diagnosis (Aase 1994). A person who is otherwise healthy may display one or two of the diagnostic traits. Furthermore, specific facial abnormalities can be subtle and difficult to recognize, their expression can change as a person ages (Aase 1994; Streissguth et al. 1991), and their severity may vary among individuals as well as among different racial and ethnic groups (Abel and Sokol 1991; Ernhart et al. 1989; May 1991; Sokol et al. 1986).

> *It is not surprising, then, that FAS is diagnosed readily at birth in only the most severely affected children and that many FAS cases go undetected at this time.*

Difficulties in Diagnosis

Clinicians face a particular dilemma in identifying and intervening with children and adults who exhibit only some of the characteristic attributes of FAS. Even though these individuals do not fulfill the diagnostic criteria for FAS, they often have behavioral (Nanson and Hiscock 1990; Streissguth et al. 1989*a,b*) and cognitive (Streissguth et al. 1991) problems that persist with age and can restrict normal functioning. "Possible fetal alcohol effects" (Clarren and Smith 1978) and "alcohol-related birth defects" (Sokol and Clarren 1989) have been suggested as descriptive terms to categorize the problems experienced by such individuals. When used appropriately in clinical practice, these terms indicate that prenatal alcohol exposure is suspected as the responsible cause for the observed abnormalities, but further proof is needed for confirmation. These terms, however, are not diagnoses. The *individual* abnormalities of FAS can develop from various genetic or environmental influences (Aase 1994), and it is nearly impossible to prove that the problems in any one child are the result of prenatal alcohol exposure.

A recent study by the Institute of Medicine (IOM; 1996) proposed five modified diagnostic categories and criteria in an effort to resolve issues that seem to be confusing to the clinical and research communities: (1) FAS with confirmed maternal alcohol exposure, (2) FAS without confirmed maternal alcohol exposure, (3) partial FAS with confirmed maternal alcohol exposure, (4) ARBD, and (5) alcohol-related neurodevelopmental disorder (ARND). Because the manifestations of FAS, ARBD, and ARND may vary in specific individuals, the study recommends that clinicians should add to a diagnosis the descriptions of patients' distinctive problems. Such information can broaden our understanding of these disorders. Even with modified diagnostic categories, however, these disorders will continue to be difficult diagnoses, and the IOM study proposes that a medical diagnosis of FAS, ARBD, and ARND should remain the purview of *dysmorphologists* and clinical geneticists.

Diagnosis of FAS in a newborn can be particularly challenging for several reasons. Because CNS dysfunction, which is a hallmark of FAS, may not be detected until several years after birth, a clinician often relies primarily on identifying the syndrome's characteristic facial features. These features, however, can be quite subtle and thus particularly difficult to recognize in the neonate. The fact that some of the distinguishing features (specifically, midfacial underdevelopment) can occur normally in many newborns (Aase 1994) and that normal swelling around the eyes in newborn infants often obscures the characteristic anomalies further complicates diagnosis within this age group (Sokol and Clarren 1989). It is not surprising,

Glossary

Axon—A part of a neuron that consists of a single fiber which carries nerve impulses from the cell body to other cells.

Basal ganglia—A group of structures deep within the brain that are involved in movement and cognition.

Cerebellum—A brain structure that is responsible for coordination of movement and posture and may have a role in some aspects of cognition.

Diencephalon—An area of the brain that encompasses the thalamus, which is the brain's relay center; the hypothalamus, which regulates the pituitary gland; and the septal area, which is related to the limbic system.

DNA—The abbreviation for deoxyribonucleic acid; the molecule that encodes the genetic information in all organisms except some viruses.

Dysmorphologist—A specialist who studies the abnormal development of tissue form.

Hippocampus—A component of the limbic system within the brain that is involved in emotional behaviors related to survival, such as flight or fright responses. The hippocampus is associated with memory, particularly with the learning of new information and of sequentially presented information.

Neocortex—A portion of the cerebral cortex that is responsible for higher mental functions, behavioral reactions, general movement, and perception.

Neural folds—Paired neural folds fuse to form the neural tube, which is a structure in the early stages of nervous system development that develops into the spinal cord and brain.

Sensory nucleus—The nucleus of termination of sensory fibers of a peripheral nerve.

Stereotypy—The persistent repetition of senseless acts or words.

Teratogen—An agent or factor that produces defects in the developing embryo.

then, that FAS is diagnosed readily at birth in only the most severely affected children and that many FAS cases go undetected at this time (Abel and Sokol 1987; Little et al. 1990; Sokol and Clarren 1989).

In older children and in adults, diagnosis also is difficult because some of the representative features become less distinctive with age. The onset of adolescence often brings a change to the characteristic slender build of children with FAS, particularly in girls (Streissguth et al. 1991). Facial appearance begins to normalize with age as continued slow growth of the face, chin, and nose through adolescence compensates for underdevelopment of the midface (Streissguth et al. 1991). Although certain characteristic features of FAS can be recognized in severely affected children even in adolescence, FAS becomes more difficult to diagnose in children with mild expression of the syndrome (Spohr et al. 1993). Because adult height and head circumference usually remain below normal, however, and abnormalities of the eyes and upper lip are seen in 80 percent of adolescents and adults with FAS, these features can be valuable for diagnosing older persons (Streissguth et al. 1991).

Normal variations of particular facial features in certain racial groups (Abel and Sokol 1991; Ernhart et al. 1989; May 1991; Sokol et al. 1986) and in particular families (Aase in press) also can influence diagnosis. For example, a moderate degree of midfacial underdevelopment is a normal feature in many Native American groups. Broader lips normally seen in African-American children may mask the thin upper lip that is seen in FAS, and the characteristic tall stature of some northern European and central African populations may obscure FAS-related growth deficiency (Aase 1994). Similarly, such family traits as IQ, height, facial features, and even creases on the palm (Streissguth et al. 1991) may be heavily influenced by heredity and can either mask or mimic the features of FAS (Aase 1994). These variations can complicate diagnostic efforts and should be considered in the diagnostic process.

Given the challenges that face diagnosticians, Abel et al. (1993) designed a study to determine whether medical providers (obstetricians and pediatricians) and biomedical researchers not formally trained in dysmorphology could accurately and consistently identify in facial photographs those infants who had and did not have FAS. Study participants in both groups generally were able to accurately identify FAS on the basis of photographs alone. Moreover, identification of FAS was highly correlated with maternal drinking behavior, thus underscoring that facial features and maternal drinking are associated. With the provision of additional information to the participants, such as birth weight, the accuracy of identification increased only among biomedical scientists. This finding suggests that the clinicians were less influenced in their evaluations by supplementary diagnostic information. The race of the photographed children, however, influenced the accuracy of identification ratings within occupational groups. African-American children were more likely than Caucasian children to be incorrectly classified as having FAS. Because all but one of the study participants were Caucasian, this bias implies that lack of knowledge of normal African-American features can influence the accuracy of diagnosis. The authors noted that the findings should be considered in light of a potential shortcoming of the study: Only photographs of children with FAS and healthy children were used. Thus, the study confirms that the participants could distinguish between normal and unusual-looking children but not necessarily between children with FAS and children with other birth defects (Abel et al. 1993).

To date, FAS is more commonly identified by an overall pattern of facial features than by specific individual facial characteristics.

To date, FAS is more commonly identified by an overall pattern of facial features than by specific individual facial characteristics (Astley et al. 1992; Clarren et al. 1987; Rostand et al. 1990). However, clinicians most frequently use the occurrence of small eye openings, smooth and long philtrum, thin upper vermilion (i.e., narrow red margin of the upper lip), increased inner canthal distance, and an elongated midface to diagnose FAS in infants and older children. An approach that employs a weighted checklist of distinguishing characteristics for FAS (Aase 1994; Smith et al. 1990; Sokol et al. 1986; Vitez et al. 1984) has proved to be of value in research and in "clinical screening" (increasing the number of appropriate referrals to diagnostic clinics), but it appears to be less effective as a diagnostic tool for clinical purposes (Aase 1994).

New Tools That Facilitate Diagnosis

Researchers are beginning to explore whether certain computer-assisted techniques may be effective tools for diagnosing FAS (Aase 1994; Astley et al. 1992). Clarren et al. (1987) performed a computer-based morphometric analysis on facial photographs of 7-year-old children who had been exposed prenatally to heavy drinking. Using this approach, the investigators were able to quantitatively define the characteristic FAS face of this age group. Sokol et al. (1991) had similar success with newborn infants.

Escobar et al. (1993) recently used computer-assisted morphometric analysis to determine whether alcohol-induced anomalies might be detected before birth. In their examination of five pregnant women, the researchers were able to identify fetal craniofacial defects that could not be recognized by routine ultrasound examination. These findings are promising, yet preliminary.

Several new avenues of research may advance efforts to improve and simplify diagnosis of alcohol-affected individuals, particularly among those who lack the facial appearance of FAS. For example, the development of a specific behavioral profile for people who are affected by prenatal alcohol exposure would lessen a clinician's reliance on clinical features and therefore could simplify diagnosis in many individuals (Aase 1994). Also, by applying imaging techniques, researchers can examine the brains of alcohol-affected individuals to detect markers of alcohol-induced injury (Mattson et al. 1992, 1994*a,b*). In pursuit of this goal, Mattson et al. (1992, 1994*a,b*) used magnetic resonance imaging[2] (MRI) to compare brain structures in four adolescents exposed in utero to heavy drinking with brain structures in normal, healthy adolescents. In the brains of the adolescents exposed to heavy drinking, MRI revealed specific structural differences among those with FAS and those who did not fulfill the criteria for FAS. The ventricles were enlarged and the basal ganglia and thalamus were smaller than these areas in the brains of the healthy controls. The cost of imaging techniques clearly makes them impractical as routine diagnostic tools; however, research applying this technology potentially can provide insight into measures that may be more effective for recognition of FAS.

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[2] Magnetic resonance imaging is an imaging technique that uses a magnetic field to produce an image of the brain. The images produced can appear as three-dimensional pictures or can be divided into two-dimensional "slices" of specific areas of interest.

Incidence of Fetal Alcohol Syndrome

For various reasons, the incidence of FAS cannot be derived with the same precision as is applied to other common birth defects. Because a simple, objective laboratory test for FAS diagnosis does not exist, diagnosis is based on recognizing anomalies described in clinical definitions, thereby posing a challenging prospect for many clinicians. Furthermore, many physicians are reluctant to diagnose a syndrome that seemingly casts a stigma on the mother and offers a child a poor prognosis that currently has, at best, extremely limited treatment options. Findings from two recent studies provide evidence of such reluctance. Studies conducted by Morse et al. (1992) and Little et al. (1990) reported that a substantial proportion of pediatricians are informed about FAS but feel unprepared or unwilling to make a differential diagnosis. These factors contribute substantially to the underreporting of FAS in medical records and influence efforts to estimate accurately the incidence of this syndrome.

... FAS occurs at a rate of 9.7 per 10,000 live births in the general obstetric population.

Researchers attempting to calculate FAS incidence have used different data sources for their estimates. Abel and Sokol (1987) surveyed 19 published worldwide epidemiologic studies on FAS frequency and estimated the incidence to be 1.9 cases per 1,000 live births. In a more recent analysis, Abel (1995) estimated that FAS occurs at a rate of 9.7 per 10,000 live births in the general obstetric population. Among heavy drinkers, 4.3 percent of children born annually have FAS, which corresponds to more than 2,000 cases each year in the United States.

Investigators at the Centers for Disease Control and Prevention (CDC) recently analyzed national Birth Defects Monitoring Program data for the years 1979 through 1992 to identify trends in FAS incidence. The data, which are abstracted from hospital discharge data of newborns, suggest that the rate of reported cases of FAS increased fourfold over this 13-year period. Furthermore, the rate of reported cases in 1993 (6.7 per 10,000 births) was six times greater than that in 1979 (1.0 per 10,000 births). Although the data seemingly suggest a dramatic increase in the rate of FAS, the investigators caution that the increase may reflect either a true increase in the number of FAS cases or an increase in primary care physicians' awareness and diagnosis of FAS in newborns (CDC 1995).

Development of Children With Fetal Alcohol Syndrome

Several investigators have conducted longitudinal followup studies to examine the physical and developmental characteristics of selected individuals diagnosed with FAS. The individuals followed in these studies generally were diagnosed with FAS at birth and, thus, usually are severely impaired. Although these studies have provided much information about the long-term effects of FAS, the information is limited by the absence of control groups in most of them, making it difficult to assess whether the observed injuries resulted solely from alcohol or from alcohol combined with other risk factors.

Recent findings from studies of adolescents and adults with FAS indicate that the deficits associated with the disorder are long lasting and pervasive. As affected children reach puberty, many of the physical characteristics of FAS become less prominent (Spohr et al. 1993; Streissguth et al. 1991). Intellectual problems, however, persist, and behavioral, emotional, and social problems become even more pronounced (Lemoine and Lemoine 1992; Streissguth et al. 1991).

Followup studies of selected individuals with FAS and ARBD in the United States (Streissguth et al. 1989*b*, 1991), France (Lemoine and Lemoine 1992), and Germany (Spohr et al. 1993; Steinhausen et al. 1993, 1994) have reported similar findings about the long-term growth, mental, and behavioral consequences associated with the syndrome. As noted earlier, many of the dysmorphic features of FAS begin to diminish with increasing age. Growth deficits also lessen: Adolescents, and particularly girls, appear to "catch up" in weight (Lemoine and Lemoine 1992; Spohr et al. 1993; Streissguth et al. 1991). In the German sample, for example, 61 percent of the boys continued to have body weights below the third percentile, compared with only 17 percent of the girls (Spohr et al. 1993). The studies suggest, however, that head circumference does not normalize as a person with FAS ages (Lemoine and Lemoine 1992; Spohr et al. 1993; Streissguth et al. 1991). Spohr et al. (1993) found that head circumference was below normal for 65 percent of the children in the German sample who were examined in a 10-year followup. Moreover, all of the children in this study who initially were diagnosed with severe FAS were microcephalic at the time of followup. The magnitude of this FAS trait is substantial, shifting the normal distribution of head circumference about two standard deviations below the population mean (Streissguth et al. 1991).

Persistence of Cognitive Deficits

Results from these studies also suggest that cognitive deficits in alcohol-affected individuals persist with age (Spohr et al. 1993; Steinhausen et al. 1993; Streissguth et al. 1991). Within the U.S. sample, 61 participants, ranging in age from 12 to 40 years, were tested to determine their IQ. The mean IQ score for the group was 68—a score that is within the mentally retarded range (Streissguth et al. 1991). Although individual scores ranged from 20 (severely retarded) to 105 (normal), 58 percent of the study participants had scores of 70 or below, the cutoff for the classification of a developmental disability requiring special education services. A wide range of IQ scores was also reported for participants in the German study (Spohr et al. 1993; Steinhausen et al. 1993, 1994). Findings from this study also suggested that IQ scores were stable over time, even with the benefit of an improved home environment.

Reading, spelling, and arithmetic performance among the U.S. study participants were at the second- to fourth-grade levels. Deficits in arithmetic skills, which were most characteristic of this group (Streissguth et al. 1991), seemingly were related to difficulty with such abstractions as time and space and cause and effect, as well as to generalizing from one situation to another and determining a situation's severity. Arithmetic deficits appeared to have an important effect on an individual's ability to live independently.

Hyperactivity appears to evolve in adolescence into problems of distractibility and of cognitive and behavioral control.

People with FAS or severe ARBD appear to have normal rote number knowledge but significant difficulty with more complex arithmetic problems, particularly estimating quantities and magnitudes of numbers. Kopera-Frye et al. (1994) tested numeric-processing ability in a group of adolescents and adults (aged 10 to 29 years) with FAS and ARBD and in a control group. The alcohol-affected individuals not only made more errors than the controls made on cognitive estimation but gave bizarre responses, such as estimating the cost of an airplane to be $3 or length of a man's spine to be 5 feet. Such problems with estimation are consistent with clinical observations that FAS patients have particular difficulty with handling money or scheduling daily activities, both of which depend on numerical estimation and reasoning (Streissguth and Randels 1988).

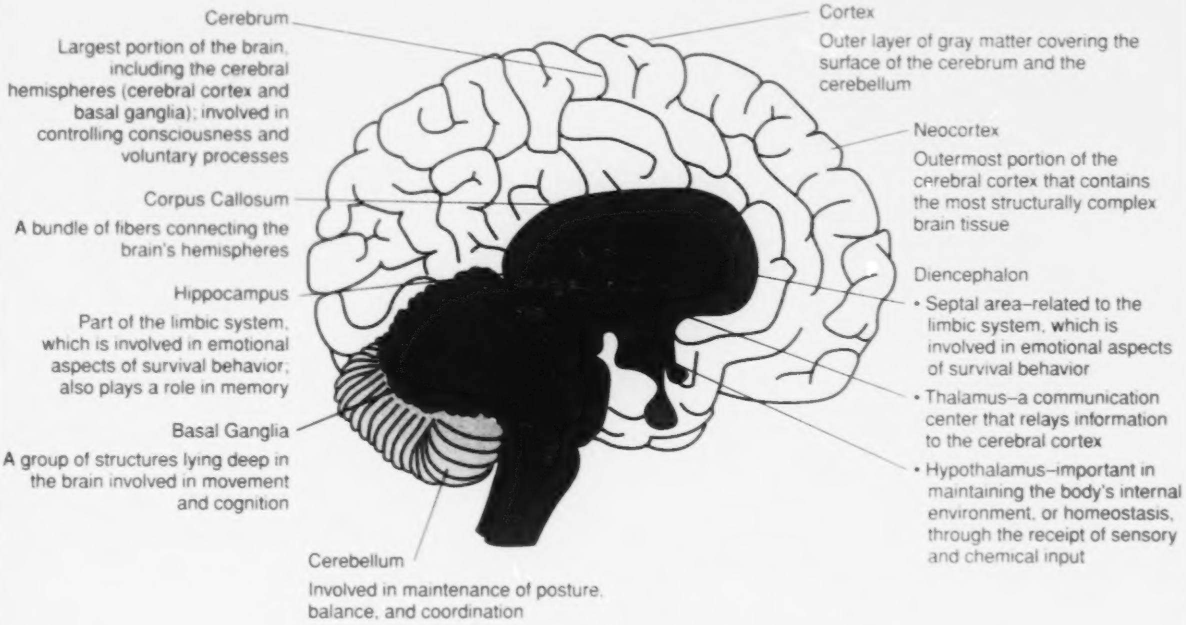
Behavior Problems

Children with FAS and ARBD are frequently described as being hyperactive and impulsive and having short attention spans (Aronson et al. 1985; Streissguth et al. 1984, 1985). Hyperactivity appears to evolve in adolescence into problems of distractibility and of cognitive and behavioral control. LaDue et al. (1992) studied 92 adolescents and adults (aged 12 to 42 years) from the U.S. followup study sample and noted that more than 70 percent were identified by their caretakers as being hyperactive and as having attention and memory problems. In addition, 42 percent had IQ scores greater than 70, but only 6 percent were in regular classes without supplemental help.

Streissguth et al. (1991) observed that maladaptive behaviors, including poor judgment, failure to consider the consequences of one's actions, and difficulty perceiving social cues, were common and characteristic of the study participants who were not classified as retarded by the IQ test. Most affected individuals functioned at approximately half their chronological age in terms of personal management and social skills, regardless of their intellectual level or the stability of their environment (Streissguth et al. 1991). Incidence of legal problems due to sexual misconduct, drunken driving without a driver's license, and shoplifting were also higher than anticipated (LaDue et al. 1992). Severe maladaptive behavior was found in 62 percent of the adolescents and adults with FAS (Streissguth et al. 1991).

In the German cohort, psychiatric assessments at preschool, school age, and adolescence indicated that although a few disorders, such as bed wetting and eating and speech disorders, are age specific and might reflect developmental delay, a variety of problems, including hyperactivity, emotional and social disorders, sleep disorders, and ***stereotypies***, may appear early in development and either persist or increase over time (Steinhausen et al. 1993, 1994). Although attention-deficit problems and social relationship problems were

Figure 1. Areas of the brain that can be damaged in utero by maternal alcohol consumption.


Cerebrum
Largest portion of the brain, including the cerebral hemispheres (cerebral cortex and basal ganglia); involved in controlling consciousness and voluntary processes
Corpus Callosum
A bundle of fibers connecting the brain's hemispheres
Hippocampus
Part of the limbic system, which is involved in emotional aspects of survival behavior; also plays a role in memory
Basal Ganglia
A group of structures lying deep in the brain involved in movement and cognition
Cerebellum
Involved in maintenance of posture, balance, and coordination
Cortex
Outer layer of gray matter covering the surface of the cerebrum and the cerebellum
Neocortex
Outermost portion of the cerebral cortex that contains the most structurally complex brain tissue
Diencephalon
• Septal area–related to the limbic system, which is involved in emotional aspects of survival behavior
• Thalamus–a communication center that relays information to the cerebral cortex
• Hypothalamus–important in maintaining the body's internal environment, or homeostasis, through the receipt of sensory and chemical input

Source: Mattson et al. 1994*a*.

most prominent in the individuals examined, most also suffered from additional emotional and behavioral problems.

Brain Development

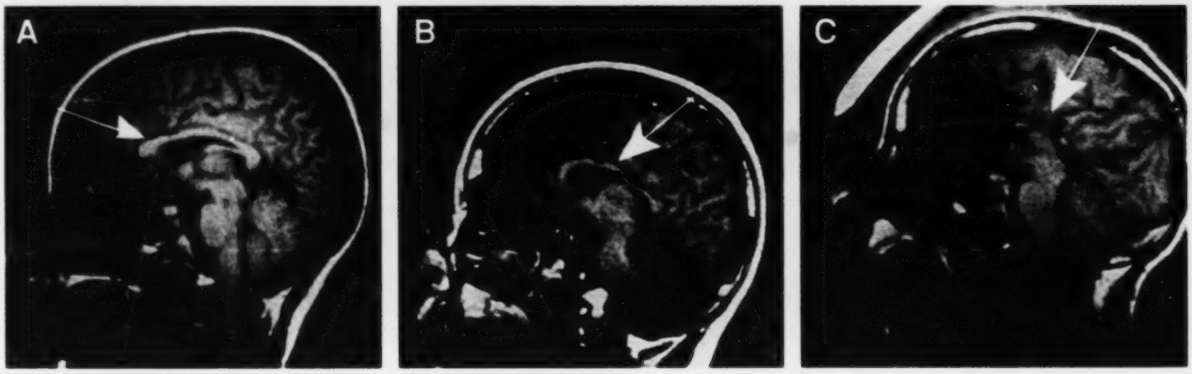
Until recently, alcohol-related structural brain abnormalities (figure 1) could be investigated only by autopsy of stillborns or premature infants who died shortly after birth. These children represent the most severe cases of alcohol-induced birth defects (Clarren 1986; Clarren et al. 1978; Jeret et al. 1987; Jones and Smith 1975). Today, the application of technologies such as MRI, which uses a magnetic field to produce an image of the brain, is enabling noninvasive examination of the brains of living children who have histories of prenatal alcohol exposure.

Mattson et al. (1992, 1994*b*) used MRI to perform volumetric analysis of the brains of four such adolescents and a control group. Two of the adolescents exposed prenatally to alcohol had FAS (Mattson et al. 1992); the other two, who did not fulfill the diagnostic criteria for FAS, had ARBD (Mattson et al. 1994*b*) (figure 2). The researchers wanted to determine whether alcohol-induced structural abnormalities in the brain occur only in individuals with FAS or also occur in individuals with ARBD. They found that the brains of all four adolescents were an average of 25 percent smaller than the brains of adolescents in the control group. The volume of the *cerebellum* was reduced by about 20 percent. The *basal ganglia* also was smaller in the four adolescents than in the controls. The proportional volume of the *diencephalon*, however, was reduced only in the two adolescents with FAS, suggesting that such an outcome may occur only in severe cases of alcohol exposure.

In a more recent study, Riley et al. (1995) used MRI to assess the corpus callosum in 13 children exposed in utero to significant amounts of alcohol (figure 3). The corpus callosum is a bundle of fibers that connect the hemispheres of the brain, thus facilitating transmission of information. In two of the children, the corpus callosum was completely absent; this is a relatively rare abnormality that occurs in about 0.1 percent of the general population. The overall area of the corpus callosum in the remaining children was significantly

Figure 2. MRIs of the brain of a healthy child and of two children with FAS.

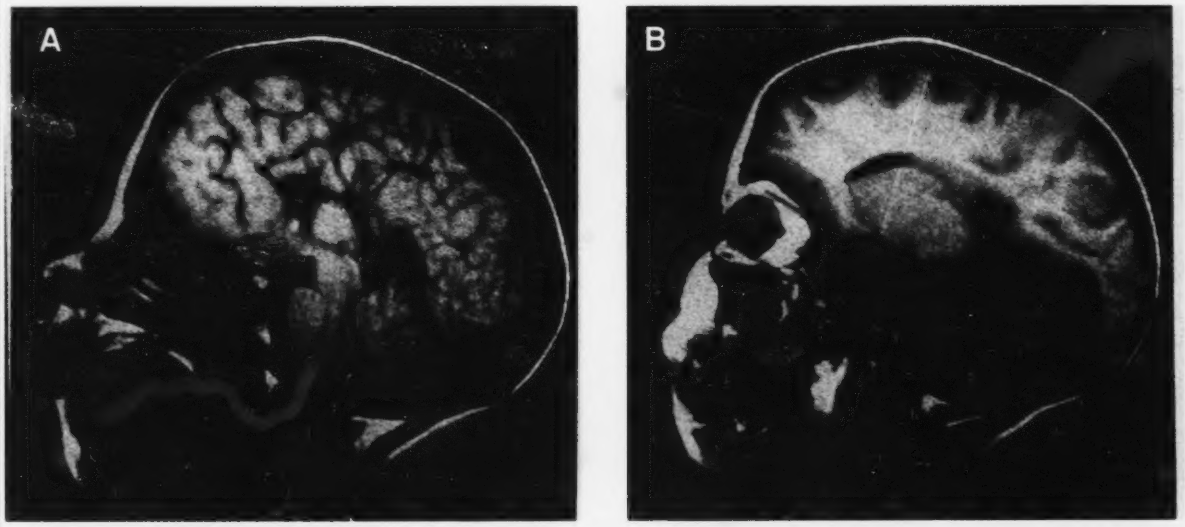
(A) MRI showing the side view of a 14-year-old control subject with a normal corpus callosum, (B) a 12-year-old with FAS and a thin corpus callosum, and (C) a 14-year-old with FAS and agenesis (i.e., absence due to abnormal development) of the corpus callosum.



Source: Mattson et al. 1994*a*.

Figure 3. MRIs of a 9-year-old girl with FAS.

(A) Midsagittal view shows agenesis of the corpus callosum.
(B) Sagittal view shows colpocephaly, a characteristic feature often associated with callosal agenesis.



Source: Riley et al. 1995. Riley, E.P.; Mattson, S.N.; Sowell, E.R.; Jernigan, T.L.; Sobel, D.F.; and Jones, K.L. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research* 19(5):1198–1202, 1995. Reprinted by permission.

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smaller than in a control group of children matched for age and gender. When the investigators divided the corpus callosum into regions (a standard approach for analyzing this structure), three of the five regions were smaller in proportion to the overall brain size in the alcohol-exposed children. The investigators suggest that the selective reduction in the area of the corpus callosum is similar to that reported in attention-deficit hyperactivity disorder (Hynd et al. 1991). Attention deficits, such as becoming easily distracted from a task, and increased activity have long been considered signs of FAS (Streissguth et al. 1986).

Other recent studies also have noted neuroanatomical abnormalities in children exposed prenatally to alcohol. Holzman et al. (1995) examined a large population-based sample of premature infants who weighed 2 kilograms or less at birth. The investigators reported an elevated risk for isolated brain hemorrhage, any brain hemorrhage, or white matter damage in infants whose mothers reported consuming at least seven drinks per week or at least three drinks per occasion during pregnancy. These injuries are the most common types of brain injuries in premature infants. Also, a study by Sowell et al. (1996) reported that children with FAS have selective reductions in the anterior vermis of the cerebellum.

Prospective Longitudinal Studies

Several prospective longitudinal studies are providing knowledge about the full spectrum of defects that may result from in utero alcohol exposure. Study findings have helped to confirm that the consequences of prenatal alcohol exposure range from the severe physical and mental impairments of FAS to the more subtle behavioral and cognitive deficits that are labeled ARBD. In contrast to the followup assessments described earlier, prospective longitudinal studies consider the scope of drinking practices among women; that is, from abstaining from alcohol to heavy consumption (commonly defined in pregnant women as more than 1 ounce of absolute alcohol, or more than two drinks, per day). Thus, such studies provide a serendipitous opportunity to measure the relationship of quantity, frequency, timing, and pattern of drinking to infant and child outcome, while statistically controlling for the numerous factors that may influence prenatal and postnatal development, including prenatal exposure to smoking and to drugs, pregnancy complications, maternal demographics, intellectual and personality characteristics, and other socioenvironmental factors. These studies also are useful resources for identifying brief intervention and treatment approaches that effectively help pregnant women to stop drinking.

The 1993 *Eighth Special Report to the U.S. Congress on Alcohol and Health* covered in great detail the findings from six core studies, namely, the Seattle Longitudinal Study on Alcohol and Pregnancy, the Detroit Longitudinal Study, the Ottawa Prenatal Prospective Study, the Cleveland Prospective Alcohol-In-Pregnancy Study, the Georgia Alcohol and Pregnancy Research Project, and the Pittsburgh Maternal Health Practices and Child Development Study. In general, these studies have reported many similar findings. Some results, however, have been inconsistent, perhaps due to differences in study designs and methodologies. The following discussion primarily addresses findings published since the preparation of the previous report.

Growth Deficits

Researchers usually assess growth in terms of weight, head circumference, and height. Using these indicators, several investigators have observed an association between prenatal alcohol exposure and growth deficits at birth; such deficits often are evident even after controlling for the influence of smoking and illicit drug use (Day et al. 1989; Greene et al. 1991*b*; J.L. Jacobson et al. 1994*b*; Russell and Skinner 1988; Smith et al. 1986; Streissguth et al. 1981). Slower growth persists in alcohol-exposed infants 6 to 8 months after birth (Geva et al. 1993; Golden et al. 1982; J.L. Jacobson et al. 1994*b*) and in children 6 years of age (Day et al. 1994; Russell et al. 1991).

Not all studies, however, have found sustained growth retardation in children exposed prenatally to alcohol. For example, Barr et al. (1984) observed growth deficits in children of the Seattle group examined at 8 months of age. In followup examinations, however, the children were not significantly smaller than their non-alcohol-exposed peers. Fried and O'Connell (1987) also reported no long-term growth deficits in alcohol-exposed children examined in the Ottawa study.

Table 1. Presence of effects of prenatal alcohol exposure among infants in six prospective longitudinal studies, as measured by the Bayley Scales of Infant Development.

Investigator (Source)	Site	Mean Number of Drinks/ Week During Pregnancy	Ounces of Absolute Alcohol/ Day	Effect?
Coles (Smith et al. 1982)	Atlanta	16.1	1.80	Yes
Streissguth (Streissguth et al. 1980)	Seattle	3.6	0.26	Yes
Fried (Fried and Watkinson 1988)	Ottawa	3.5	0.25	No*
Jacobson, Jacobson, and Sokol (J.L. Jacobson et al. 1993)	Detroit	3.2	0.23	Yes
Day (Richardson et al. 1995)	Pittsburgh	1.0	0.07	No
Ernhart and Sokol (Greene et al. 1991*a*)	Cleveland	1.0	0.07	No

*Effect was significant until controlled for smoking.

Cognitive and Behavioral Findings in Infants

Most prospective studies on the effects of prenatal alcohol exposure have used the Bayley (1969) Scales of Infant Development, an instrument that measures age-appropriate mental and psychomotor development. Table 1 summarizes the results from the six prospective longitudinal studies mentioned earlier. In the Atlanta study, which examined pregnancy outcome in a highly disadvantaged group of women, researchers observed mental and motor deficits in infants born to heavy drinkers (women who consumed an average of 1.8 ounces of absolute alcohol per day) who continued to drink throughout pregnancy (Smith al. 1986). Deficits also were reported in infants born to moderate drinkers (women who consumed an average of 0.26 ounce of absolute alcohol per day) of the predominately white, middle class sample of women in the Seattle study (Streissguth et al. 1980) and to moderate drinkers (women who consumed an average of 0.23 ounce of absolute alcohol per day) of the economically disadvantaged African-American sample of women examined in the Detroit study (J.L. Jacobson et al. 1993). Deficits were not reported in alcohol-exposed children in the Cleveland (Greene et al. 1991*a*) or the Pittsburgh studies (Richardson and Day 1991; Richardson et al. 1989). The mothers in both of these studies, however, consumed an average of 0.07 ounce of alcohol per day during pregnancy, an amount lower than amounts noted in the Atlanta, Seattle, or Detroit study populations. Results from the Ottawa study reported alcohol effects as measured by the Bayley Scales, but these findings were confounded by maternal smoking in this study sample (Fried and Watkinson 1988).

To better understand the apparent discrepancy among these findings, investigators in the Detroit study examined Bayley scores in terms of the incidence of poor performance, defined as a score in the bottom 10th percentile of the distribution (J.L. Jacobson et al. 1993). They found that the incidence of poor motor performance more than doubled among infants born to moderate-to-heavy drinkers (women who drank at least 0.5 ounce of absolute alcohol per day, or about one standard drink per day during pregnancy). A review of the studies in which Bayley deficits were not found suggests an insufficient number of infants whose mothers drank above the level of 0.5 ounce of absolute alcohol per day (S.W. Jacobson in press *b*). For example, although a substantial number of mothers in the Pittsburgh study (Day et al. 1989) drank at moderate-to-heavy levels during the first trimester, most reduced their drinking to very low levels in the second and third trimesters, when learning and motor impairment are more likely to occur in the fetus (West and Pierce 1986). Similarly, the Cleveland sample included only 7 infants whose mothers drank above the 0.5-ounce level (Greene et al. 1991*a*), compared with 45 infants in the Detroit cohort. When all but seven of the infants whose mothers drank more than 0.5 ounce of absolute alcohol per day were randomly deleted from the Detroit population—thus tailoring the Detroit sample to parallel the Cleveland sample—no significant correlation between alcohol and motor development deficits was found (Jacobson and Jacobson 1996).

Processing Speed

Attention deficits are the most consistent neurobehavioral effect of prenatal alcohol exposure in older children. Shaywitz et al. (1980) first reported such deficits in a retrospective study that examined the effects of prenatal alcohol exposure. Prospective studies also have described attention deficits in alcohol-exposed children. For example, in the Seattle study, 4- and 7-year-old children exposed to moderate levels of exposure had poorer accuracy and slower reaction times (a measure of cognitive proficiency) (Streissguth et al. 1984, 1986). These findings, together with data from other tests involving reaction time, led Streissguth et al. (1984, 1986) to suggest that alcohol-exposed children suffer from an alcohol-related deficit in speed of central processing.

To further explore this hypothesis, investigators in the Detroit longitudinal study assessed processing speed in infancy by using three assessment tests: the Fagan recognition memory test (Fagan and Singer 1983); a test of cross-modal transfer of information (Rose et al. 1978); and a visual expectancy test, which assesses reaction time in infancy (Haith et al. 1988). The recognition memory and cross-modal tests used the infants' length of visual fixation to measure processing speed (Colombo and Mitchell 1990), with short looks believed to both reflect more rapid information processing and predict higher childhood IQ (Colombo et al. 1989). The visual expectancy test measured an infant's reaction time in shifting gaze back and forth in response to an image flashing in alternating left-right positions.

The researchers found that maternal drinking during pregnancy was associated with a pattern of longer visual gaze and slower reaction times, suggesting that the slower, less efficient information processing reported in older children is already evident in infants (S.W. Jacobson et al. 1993, 1994). This effect was dose dependent and seen at 6.5 and 12 months of age. The effect of prenatal alcohol exposure on recognition memory in infants was specific and seen solely on measures of processing speed (S.W. Jacobson in press *a*). Infant reaction time proved to be a particularly sensitive indicator of alcohol-related effects on processing speed. This measure detected deficits at maternal consumption levels of 0.5 ounce of absolute alcohol per day (S.W. Jacobson et al. 1994), the lowest level at which effects have been detected.

Attention deficits are the most consistent neurobehavioral effect of prenatal alcohol exposure in older children.

Cognitive and Attentional Effects in Childhood and Adolescence

Longitudinal examination of the Seattle study sample has shown that the consequences of maternal drinking during pregnancy are still measurable 14 years later as attention and performance deficits in the alcohol-exposed children (Streissguth et al. 1994*b,e*). In the 14-year followup, maternal alcohol use was related to poorer phonetically based reading and arithmetic performance in the adolescents examined. The effects generally were dose dependent and were most pronounced in adolescents exposed prenatally to binge-drinking patterns (defined as more than five drinks per occasion) (Streissguth et al. 1994*a*). The effect of binge drinking in the Seattle study is consistent with experimental animal studies showing that higher maternal blood alcohol concentrations are more damaging than the same exposure over a longer period of time (e.g., Pierce and West 1986; Schenker et al. 1990; West et al. 1989).

Reading and arithmetic scores for the individuals studied were moderately related to the scores obtained at 7 years of age. Furthermore, the children of heavy drinkers who performed poorly on arithmetic tests at 7 years were more likely than children of abstainers to perform poorly at 14 years, suggesting that the observed deficits in the alcohol-exposed children reflect an ongoing compromise of CNS function (Streissguth et al. 1994*b,e*).

Attention and memory problems also were observed in the individuals studied. In particular, alcohol exposure appeared to affect attention states, response inhibition, and spatial learning (Streissguth et al. 1994*b,e*). The spatial-learning deficits observed in these adolescents resemble deficits found in experiments with alcohol-exposed laboratory animals that have lesions in the ***hippocampus*** of the brain (Goodlett et al. 1987; Riley et al. 1986).

Followup examinations in the Atlanta study revealed that at school age (6 years), the children displayed specific cognitive deficits. The most obvious deficits were present in children exposed to alcohol throughout pregnancy. Coles et al. (1991) reported that alcohol exposure during any part of pregnancy was associated with poorer academic achievement. Exposure during the third trimester of pregnancy, however, was particularly associated with lower aptitude scores and significant decrements in sequential processing of information. Most children studied in this group, however, could not be classified as mentally retarded.

A correlation between pregnancy drinking and cognitive function usually is interpreted as resulting from the direct effect of alcohol on CNS development in a fetus.

Comparisons With Attention-Deficit Hyperactivity Disorder

As described earlier, children exposed prenatally to alcohol often are hyperactive, distractible, and impulsive and have short attention spans (Streissguth et al. 1984, 1985)—behaviors that are similar to those observed in children with attention-deficit disorder (ADD). The extent to which alcohol-related attention deficits are similar to those seen in children with ADD is unclear. Nanson and Hiscock (1990) compared the levels of activity and attention in a group of children with FAS or ARBD with the same features in a group of children with ADD and in a control group. They found that the children with ADD responded faster than the children with FAS. However, both the children with FAS and the children with ADD made more impulsive errors than the children in the control group, and parents rated both groups of children similarly on behavioral rating scales (Nanson and Hiscock 1990). These investigators suggested that treatment strategies designed to facilitate attention and learning in ADD children may benefit alcohol-affected children.

Investigators in the Atlanta study (Brown et al. 1991) confirmed earlier findings from the Seattle study (Streissguth et al. 1984, 1986) of sustained attentional deficits in children whose mothers drank throughout pregnancy. However, the Atlanta investigators found little evidence of impulsivity in these children (Brown et al. 1991). Teachers described the Atlanta children as having attention and behavioral problems. Although the behaviors were consistent with the diagnostic symptoms for attention-deficit hyperactivity disorder (ADHD), they were not sufficiently elevated for such a diagnosis. In addition, the behaviors deviated from the usual pattern of impulsivity associated with ADHD. Vigilance test performance of 17 children with FAS or ARBD and 57 nondysmorphic, alcohol-exposed children in the Atlanta group was more similar to the performance of controls than to that of children with ADHD, who were less attentive, slower, and more impulsive, as evidenced by more errors of commission (Coles et al. 1994). In contrast, investigators from the Seattle study reported that prenatal alcohol exposure was associated with more errors of omission and commission in children aged 4, 7.5, and 14 years (Streissguth et al. 1984, 1986, 1994*b*.)

Post Partum Maternal Drinking

A correlation between pregnancy drinking and cognitive function usually is interpreted as resulting from the direct effect of alcohol on CNS development in a fetus. The observed deficit, however, also may be due to, or exacerbated by, the socioenvironmental effect on the child of being raised by a drinking mother. Such an effect can be evaluated in research studies by examining the relationship of the deficit to post partum maternal alcohol use. Unfortunately, maternal drinking during and after pregnancy often is highly confounded by other factors, and, therefore, it may not always be possible to determine the degree to which observed deficits are due to direct effects of alcohol or to socioenvironmental factors. The inclusion of both factors in multivariate statistical analyses may obscure true prenatal effects.

Statistical analysis of data from the Detroit study indicated that drinking by the mother after the birth or by the caregiver had little or no influence on the neurobehavioral deficits detected during infancy. Rather, such deficits appeared to be related specifically to prenatal alcohol exposure (J.L. Jacobson et al. 1993; S.W. Jacobson et al. 1993, 1994). Researchers of the Atlanta study reported similar findings: The deficits in intellectual functioning seen in the children who were exposed to heavy maternal drinking throughout pregnancy were evident, even after investigators statistically controlled for current drinking by caregivers (Coles et al. 1991). These children also were more often described as showing higher levels of externalizing behaviors, including destructive, inattentive, aggressive, and nervous or overactive behavior, as well as inappropriate social behavior and poor social competence. These behaviors also persisted after researchers controlled for the influence of caregivers' drinking (Brown et al. 1991). By contrast, depression in the children appeared to be attributable, at least in part, to problems in the postnatal environment. Thus, although some secondary psychopathologies or deficits can be attributed to socioemotional consequences of being raised by an alcohol-abusing mother, a number of specific cognitive and behavioral deficits associated with prenatal alcohol exposure appear to reflect CNS damage. Further research is needed to determine definitively the effects of postnatal environment on children exposed prenatally to alcohol.

Researchers theorize that alcohol exposure at certain periods and doses during pregnancy will determine the defects observed in a child at birth and beyond.

Timing of Fetal Exposure to Alcohol

Experimental research has confirmed the teratogenic effects of alcohol; however, studies have yet to reveal fully how the timing of a mother's drinking and the duration of a fetus' exposure disrupt particular stages of fetal development. In general, researchers theorize that because fetal development is sequenced throughout pregnancy, alcohol exposure at certain periods and doses during pregnancy will determine the defects observed in a child at birth and beyond (figure 4). Determining the exact stage of exposure and specific dose that is associated with particular defects can be challenging in clinical studies because maternal consumption levels and timing of use are provided by the relatively inaccurate measure of a mother's self-report.

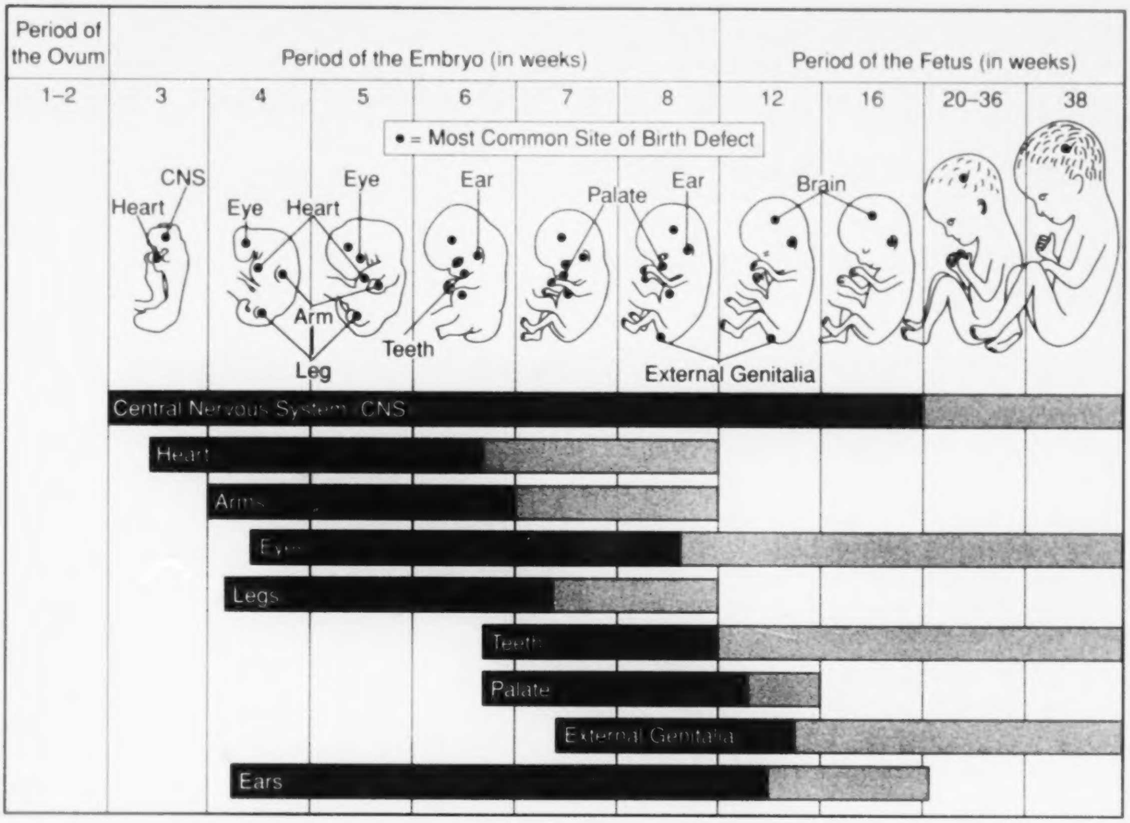
In animal studies, researchers can control for the numerous variables encountered in clinical studies (e.g., varying patterns and levels of drinking throughout pregnancy confounding factors such as smoking and nutrition), thus enabling more precise measures of the effects of alcohol at various levels and periods of exposure. Findings from these studies suggest that first-trimester exposure is associated with dysmorphia and neurological damage (Sulik and Johnston 1983). However, the central nervous system (CNS) is sensitive to alcohol exposure during a prolonged developmental period and, thus, can be affected even when exposure occurs only during the later part of pregnancy (Miller 1992; West and Goodlett 1990). The pattern of exposure also is an important factor. A recent animal study by Goodlett and Peterson (1995) demonstrated that binge-like exposure to alcohol during particular periods of gestation caused specific structural and behavioral deficits in the fetus.

As noted earlier, findings from several longitudinal clinical studies indicate that first-trimester exposure to alcohol is associated with craniofacial anomalies in children (Coles et al. 1985; Day et al. 1989; Ernhart et al. 1987; Graham et al. 1988). According to these studies, prenatal exposure also adversely affects growth. Findings from these studies, however, have been inconsistent in terms of periods of exposure that are critical to this outcome. Such inconsistencies may arise due to varying doses of exposure and postnatal stressors, including home environment and nutrition, in the different longitudinal studies. Day et al. (1989) reported that women in the Pittsburgh study who drank during the first or second trimester or both were at increased risk of having a low birth-weight infant. Deficits in length and head circumference measurements at birth also were associated with early first-trimester drinking. In the Atlanta study, neonatal growth deficits were observed in infants born to women who drank *throughout* pregnancy; however, children born to women who stopped drinking at the beginning of the second trimester approached the level of growth of non-alcohol-exposed infants (Coles et al. 1985). Coles (1994) suggests that, based on these findings, growth deficits at birth may occur when a mother drinks during the third trimester of pregnancy—a time when the fetus is growing rapidly. However, stopping alcohol use later in pregnancy may allow an adversely affected fetus to catch up on growth.

Some results indicate that timing of in utero exposure to alcohol also may affect postnatal growth. Findings from the Pittsburgh study suggest a relationship between alcohol exposure in later pregnancy and growth deficits in children examined at 8 months (Day et al. 1990),

Figure 4. Vulnerability of the fetus to defects during different periods of development.

The black portion of the bars represents the most sensitive periods of development, during which teratogenic effects on the sites listed would result in major structural abnormalities in the child. The gray portion of the bars represents periods of development during which physiologic defects and minor structural abnormalities would occur.



Source: Adapted from Moore and Persaud 1993. *The Developing Human: Clinically Oriented Embryology.* © W.B. Saunders Co., Philadelphia. Page 156. Reprinted by permission.

18 months (Day et al. 1991*a*), 3 years (Day et al. 1991*b*), and 6 years (Day et al. 1994). The Detroit study, in a followup examination of children at 6 months of age, reported similar findings (J.L. Jacobson et al. 1994*b*). Data from the Atlanta study showed that weight and stature of school-age children (5 to 7 years) exposed to alcohol throughout pregnancy were similar to measurements in non-alcohol-exposed children; however, deficits in head circumference observed at birth in the children exposed to alcohol persisted at the time of reexamination. This effect is consistent with findings from animal studies that noted deficits in head circumference of animals exposed to alcohol during the brain growth spurt (West and Goodlett 1990).

Results from longitudinal studies also have demonstrated critical periods of exposure for alcohol-induced neurobehavioral effects. In a longitudinal study of children born to women treated in a Helsinki prenatal clinic, investigators found that during the 2-year followup of the children, heavy alcohol exposure in the first trimester alone had no definite effect on mental or language development (Autti-Ramo et al. 1992). Exposure to heavy use during the first and second trimesters, however, increased the occurrence of delayed language development in the children. Similar observations were reported in the Atlanta study (Coles et al. 1991). School-age children (5 to 8 years) whose mothers had continued to drink throughout pregnancy had poorer

Table 2. Drinking levels[*] in ounces of absolute alcohol per day and number of standard drinks[†] per day.

Drinking Level	Ounces of Absolute Alcohol/Day	Number of Standard Drinks/Day
Abstainer	0	0
Light	0.01–0.49	0.02–0.99
Moderate	0.50–0.99	1.00–1.99
Heavy	1.0+	2.00–3.99

[*] Drinking levels are from the National Institutes of Health 1988 National Health Interview Survey.
[†] One standard drink ≅ 0.5 oz absolute alcohol ≅ 12 oz beer ≅ 5 oz wine ≅ 1.25 oz liquor.

sequential information processing and academic achievement than those whose mothers stopped drinking in the second trimester. Problems were noted in short-term memory, math skills, and decoding of letters and words. The lack of effects in the Pittsburgh sample as measured by the Bayley Scales (Richardson and Day 1991; Richardson et al. 1989) also suggests that neurobehavioral effects are more likely related to exposure to alcohol later in pregnancy. In this group, a high proportion of women reported moderate first-trimester drinking, yet very few drank at moderate or heavy levels during the second or third trimesters. Moderate first-trimester exposure alone apparently was not sufficient to produce Bayley deficits.

> *This finding suggests that a considerably higher dose of alcohol is necessary to disrupt psychomotor development than infant cognitive function.*

Dose Response

Dose-response patterns usually are evaluated in research studies by dividing levels of consumption (measured as ounces of absolute alcohol per day) into discrete groups that are determined a priori and comparing group means for various outcomes after statistically adjusting the data for potential confounders. A dose-response relationship is inferred if the adjusted means scores increase or decrease with increasing levels of alcohol exposure. Consumption levels from the 1988 National Health Interview Survey, as defined in table 2, have been used to create exposure groups in some longitudinal studies (Jacobson and Jacobson 1994).

According to Vorhees (1986), neurobehavioral outcomes appear to be the most sensitive index of the fetal toxicity, or teratogenicity, of a substance that affects multiple developmental domains. This idea supports a behavioral teratology model of a continuum of alcohol-induced impairment, in which intellectual and behavioral effects can occur even in the absence of obvious dysmorphology or abnormal growth (Vorhees 1986). For example, Autti-Ramo et al. (1992) found that 60 percent of the children exposed to heavy prenatal alcohol consumption in their study met criteria for CNS dysfunction, whereas 47 percent met criteria for growth retardation and only 10 percent for craniofacial anomalies.

In the Detroit study, the effect of prenatal alcohol exposure as measured by the Bayley Mental Development Index (a part of the Bayley Scales of Infant Development that measures age-appropriate cognition, fine motor coordination, and language skills) was dose dependent, with data suggesting that even low levels of alcohol produced an effect (J.L. Jacobson et al. 1993). The incidence of poor performance increased among the children at exposure levels as low as 0.5 ounce of absolute alcohol per day, a level of drinking at which most mothers scored negative for alcohol abuse problems on the Michigan Alcoholism Screening Test (MAST) discussed later (Selzer 1971). In contrast, the effect of alcohol as measured by the Bayley Psychomotor Development Index (a measure of gross motor development) was not dose dependent, with scores reduced only at the highest level of exposure; that is, 2 ounces of absolute alcohol per day. This finding suggests that a considerably higher dose of alcohol is necessary to disrupt psychomotor development than infant cognitive function.

In a review of human studies evaluating dose-response effects of alcohol, Jacobson and Jacobson (1994) proposed that most neurobehavioral effects appear to have thresholds ranging from 0.5 ounce to 2.0 ounces of absolute alcohol per day (or 7 to 28 standard drinks per week)(table 3). According to the data analyzed, although some measures such as reaction times at 4 and 7 years of age were found to have no threshold, 0.5 ounce of

Table 3. Thresholds of maternal alcohol consumption at which neurobehavioral effects were seen in two cohorts of children.

Ounces of Absolute Alcohol/Day	Neurobehavioral Outcome	Age of Children at Measurement
	Seattle Cohort	
Prior to pregnancy recognition		
2.0	Delayed mental development	8 months[*]
	Delayed gross motor development	8 months[*]
	Greater impulsivity	7 years[†]
1.5	Lower IQ scores	4 years[‡]
	Poorer fine motor coordination	4 years[§]
	Poorer sustained attention	7 years[†]
1.0	Poorer sustained attention	4 years[‖]
0.5	Poorer fine motor coordination	4 years[§]
Midpregnancy		
2.0	Poorer habituation	1–2 days[¶]
1.5	Poorer spatial relations	4 years[§]
1.0	Lower IQ scores	7 years[**]
No threshold (<0.5)	Slower reaction times	4 and 7 years[†§‖]
	More impulsive behavior	4 years[‖]
	Poorer gross motor balance	4 years[§]
	Detroit Cohort	
During pregnancy		
2.0	Delayed gross motor development	13 months[††]
	Sustained directed activity	12 months[‡‡]
1.0	Slower information-processing speed	6.5 and 12 months[‡‡]
0.5	Delayed mental development—bottom 10%	13 months[††]
	Slower reaction time	6.5 months[§§]
	Smaller proportion of fast responses	6.5 months[§§]
No threshold (<0.5)	Delayed mental development	13 months[††]
	Less complex play	12 months[‡‡]

[*] Streissguth et al. 1980.
[†] Streissguth et al. 1986.
[‡] Streissguth et al. 1989*b*.
[§] Barr et al. 1990.
[‖] Streissguth et al. 1984.
[¶] Streissguth et al. 1983.
[**] Streissguth et al. 1990.
[††] J.L. Jacobson et al. 1993.
[‡‡] S.W. Jacobson et al. 1993.
[§§] S.W. Jacobson et al. 1994.

absolute alcohol per day (or one drink per day) may be a lower bound threshold for neurobehavioral effects. This finding is supported by the fact that studies that have included very few mothers who drank at or above that level (Greene et al. 1991*a*) have generally failed to detect effects on neurobehavioral development. The authors note, however, that even if no functional deficits are associated with a given level of alcohol exposure in infancy and childhood, there is potential for unobservable neuroanatomical damage. Animal studies suggest that such damage could lead to functional deficits that can be detected only under challenging or stressful conditions (Riley 1990).

Evidence that mothers report higher levels of drinking retrospectively than during pregnancy (Ernhart et al. 1988; S.W. Jacobson et al. 1991; Robles and Day 1990; Tlucak-Morrow et al. 1989) has raised some concern that alcohol levels reported during pregnancy may systematically understate the degree of fetal exposure. If so, effects occurring only in cases of heavy consumption might be mistakenly attributed to moderate pregnancy drinking (Kaminski 1992). Investigators in the Detroit study compared the validity of concurrent and retrospective reports of pregnancy drinking in relation to effects on infant outcome. Although higher drinking levels were reported retrospectively, only the concurrent reports related to smaller birth size, slower postnatal growth, and poorer performance on infant tests of cognition and information-processing ability (S.W. Jacobson et al. in press *c*). These findings suggest that interviews during pregnancy may provide valid information and that threshold values of alcohol derived from concurrent reports are likely therefore to be reasonably accurate.

> *... most neurobehavioral effects appear to have thresholds ranging from 0.5 ounce to 2.0 ounces of absolute alcohol per day (or 7 to 28 standard drinks per week).*

Drinking Patterns

Although most studies quantify alcohol intake in terms of mean ounces of absolute alcohol per day averaged across pregnancy, this measure may obscure the importance of drinking patterns and concentration of alcohol exposure at a given time. Most maternal drinking during pregnancy appears to be concentrated in a few days each week (Sokol et al. 1986). For example, in the Detroit study, only 1 of 480 mothers actually drank every day and only 3 drank more than 4 days each week (S.W. Jacobson in press *b*). A mean exposure of 0.5 ounce of absolute alcohol per day typically represented higher doses of alcohol on actual drinking days. For the mothers who were classified in the study as drinking at least 0.5 ounce of absolute alcohol per day—the lowest level at which deficits were consistently seen—the typical, or median, drinking pattern was 3.0 ounces of absolute alcohol per day (or six standard drinks) on an average of 2.3 days of the week. In comparison, women who drank an average of less than 0.5 ounce of alcohol per day exposed their children to a median of less than 1.0 ounce once every 3 weeks. These data are consistent with other studies in which much of the impairment appears to be related to relatively high levels of drinking per occasion (e.g., Sampson et al. 1989; Streissguth et al. 1989*a*, 1990, 1993, 1994*a,b*), a finding similar to that reported in animal studies (West et al. 1989).

Findings from the Detroit study demonstrated that adverse effects on neurobehavior were by no means limited to the children of alcoholic mothers. Most Detroit mothers who drank more than 0.5 ounce of absolute alcohol per day were negative on the MAST (Selzer 1971). This result indicates that their drinking was not marked by the psychosocial sequelae of alcohol abuse. Moreover, the 0.5 ounce of absolute alcohol per day threshold represents a sample average, and more sensitive and reliable tests may detect even lower thresholds in the future. In light of individual differences in vulnerability to prenatal alcohol exposure and in the absence of information on synergistic effects with other substances, the 0.5 ounce of absolute alcohol per day threshold should not be taken to imply that drinking below that level is "safe."

Experimental studies with laboratory animals have shown that alcohol is most damaging to the brain and increases the severity of behavioral deficits when consumption is concentrated in a short period of time (Bonthius and West 1990; Goodlett and Peterson 1995; West and Goodlett 1990). Consistent with these data are findings from the Seattle study showing that number of drinks per occasion was the strongest single predictor of adverse alcohol effects in alcohol-exposed children examined at both 7.5 and 14 years of age (Streissguth et al. 1990, 1993, 1994*a,e*). Although some investigators have suggested that chronic heavy drinking is responsible for most effects, animal studies have shown that maternal bingeing on as few as 3 days during a critical period of development can lead to physical and neurobehavioral impairment in offspring (Goodlett and Peterson 1995).

Differences in Vulnerability

FAS has been identified only in children who were heavily exposed to alcohol prenatally. However, not all women who drink excessively during pregnancy cause obvious harm to their children. Although evidence indicates that a pregnant woman's heavy drinking increases the risk for FAS in her child (Sokol et al. 1980), only 4.3 percent of alcohol-dependent women have infants with FAS (Abel 1995). Such data suggest that there are marked individual differences in vulnerability to FAS. According to findings from human and animal studies, such vulnerability results from the influence of various biological and environmental factors as well as the doses and timing of prenatal alcohol exposure.

Findings from a recent study suggest that the severity of alcoholism in pregnant women may influence the severity of FAS in their offspring.

There is some evidence that increasing maternal age is an important determinant of this differential vulnerability. Case studies of Caucasian and Native American multiparous women who have children with FAS or FAE reveal that each successive child born to these women is almost always more severely impaired than the previous one (Abel 1988; Majewski 1993; May 1991). Although maternal age and parity are difficult to separate in clinical studies, experiments with laboratory animals suggest that the increased risk of impairment is associated with aging rather than number of pregnancies per se (Abel and Dintcheff 1984, 1985; Vorhees 1988).

Some populations seemingly are at greater risk for FAS. Findings from epidemiologic studies indicate that the risk may be seven times greater among African Americans than among whites (Sokol et al. 1986). Among Native Americans, the incidence of FAS is more than 30 times that for whites, although incidence varies considerably among different American Indian communities (Chávez et al. 1988). The high prevalence of FAS in Native Americans may be skewed by overrepresentation of specific heavy-drinking tribes and differential screening (Chávez et al. 1988; May 1991; May and Hymbaugh 1989). Abel and Hannigan (1995) have argued that ethnic differences in vulnerability may result from different patterns of intake among pregnant women and from low socioeconomic status (presumably due in part to the poorer nutrition and health care available to these groups). For example, several investigators have reported that African-American and Native American alcohol-dependent women are more likely to concentrate their intake in fewer but more prolonged drinking bouts than their Caucasian counterparts, who tend to spread their alcohol intake throughout the week (Harper and Dawkins 1983; May et al. 1983). Regarding the influence of socioeconomic status, Abel and Hannigan (1995) assert that although FAS occurs in all racial groups, its incidence is greater in populations with low socioeconomic status, regardless of race. In more racially homogeneous and predominately Caucasian countries, children with FAS are nonetheless predominately from low socioeconomic status backgrounds (Abel 1995). More research is needed, however, before it can be concluded that a relationship exists between FAS and socioeconomic status.

Genetic influences also play a role in differential vulnerability to FAS. Streissguth and Dehaene (1993) studied 16 cases of twins exposed prenatally to alcohol. The diagnosis of FAS was concordant for 5 of the 5 monozygotic pairs, compared with 7 of the 11 dizygotic pairs. These outcomes occurred despite presumably equivalent exposure to alcohol within each pair (Streissguth and Dehaene 1993). Genetic vulnerability to alcohol's effects also has been demonstrated in studies of various inbred rodent strains (Goodlett et al. 1989) and selectively bred mice (Gilliam and Irtenkauf 1990).

Findings from a recent study suggest that the severity of alcoholism in pregnant women may influence the severity of FAS in their offspring. According to Majewski (1993), the severity of FAS depends more on maternal stage of alcohol illness (assessed using Jellinek's criteria[3]) (Jellinek 1960) than on the absolute quantity of alcohol consumed. However, heavy drinking during pregnancy is a necessary condition for the syndrome; two mothers of children with FAS who were successfully treated and abstained from drinking during pregnancy gave birth to normal children (see also May 1991).

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[3] Jellinek defined alcoholism as any use of alcoholic beverages that causes any damage to the individual, society, or both. The Jellinek definition divides alcoholism into five subcategories, two of which describe a disease and three of which describe problem drinking.

The traditional teratological model involves a biological insult in utero, which leads to deficits in childhood that can be detected after controlling for potential confounders. A broader view is that long-term developmental effects are the result of an interaction between the initial insult and comorbid environmental factors, or "moderator variables," that sustain the initial teratological damage or contribute to its emergence (Garmezy 1987; Rutter 1987). Few teratological studies have tested a moderator variable model, although Streissguth et al. (1990) found that the effect of prenatal alcohol exposure on IQ was exacerbated by lower paternal education and by a larger number of children in the household. Autti-Ramo et al. (1992) also found that higher socioeconomic status at the time of assessment was associated with improved Bayley and language scores for the alcohol-exposed but not the non-alcohol-exposed group. Additional research is needed to examine the degree to which moderator variables influence outcomes differentially among alcohol-exposed versus non-alcohol-exposed children. In addition, more studies are needed to identify and characterize the circumstances that may increase a child's vulnerability to the negative effects of prenatal alcohol exposure or protect a child from more severe adverse outcomes.

Alcohol-induced birth defects are completely preventable if women abstain from drinking alcohol during pregnancy.

Prevention of Alcohol-Induced Birth Defects

Alcohol-induced birth defects are completely preventable if women abstain from drinking alcohol during pregnancy. Efforts to prevent them have the primary goal to modify, on an individual and community level, the drinking behaviors of pregnant women and women of childbearing ages. Women who drink belong to different racial, ethnic, and socioeconomic segments of society, and their drinking is influenced by multiple factors. Accordingly, it is unlikely that one prevention approach can be responsive to all the factors that contribute to high-risk drinking. Rather, researchers are working toward developing multilevel strategies that, optimally, can interact to enhance prevention outcome. Within this multilevel approach are community education programs to increase general awareness of the hazards of drinking during pregnancy, approaches to effectively identify women whose drinking places them at risk for adverse pregnancy outcomes, and strategies aimed at intervening with individual women who are problem drinkers and at greatest risk for having a child who is adversely affected by alcohol.

Beverage Labeling

Warning labels, which appear on all alcoholic beverages sold or distributed in this country in accordance with Public Law 100–690, are a passive prevention measure that aims to warn a wide audience about the risks related to alcohol consumption. One of the warnings on the label addresses pregnant women and states that "According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects." The label has been in place for 7 years, and researchers are now conducting studies to evaluate its effects.

In one study, Hankin (1994) examined the effectiveness of the warning labels on pregnant women in a large African-American, inner-city sample, which is a population not likely to be reached by other public health prevention efforts. The study sample consisted of 3,572 inner-city women who began prenatal care between June 1, 1989, and September 30, 1991. Hankin et al. (1993*b*) reported a high rate of false positives, consistent with other studies of warning label awareness (Hilton 1993); 31 percent reported seeing the label in June 1989, 5 months before the label appeared on beverage containers. Hankin (1994) suggests that the false positives resulted from the interviewees' determination that an interviewer would not ask the question unless it was true, generalization of other warning labels (such as those on cigarette packaging) to alcohol, or awareness of sulfite warnings on some wine bottles (Hankin et al. 1993*b*).

Time-series analyses indicated that nonrisk drinkers reduced their drinking by 0.05 ounce of absolute alcohol per week after the warning label was implemented (Hankin et al. 1993*a*, 1994*a*) but that risk drinkers did not change their drinking patterns, a finding consistent with data reported by Andrews et al. (1991). After extending the study through June 1993, Hankin et al. (1994*b*) reported that even light drinkers who initially responded to the warning label began to become accustomed to it and suggested that the label effect may be short lived. (Also see Chapter 9, Prevention of Alcohol Problems, for a discussion of this topic.)

Awareness of the Hazards of Drinking During Pregnancy

Educating communities, particularly expectant mothers, about the hazards associated with drinking during pregnancy is an important part of the effort to prevent FAS and ARBD. Two national surveys conducted in 1985 and 1990, before the introduction of alcoholic beverage warning labels in 1990, aimed to determine how much women and men knew about the risks of drinking during pregnancy, how knowledge levels changed over the 5-year period, and what the implications of these findings were with regard to reducing the level of FAS among newborns. Survey findings indicated that most women believed that heavy drinking during pregnancy increases the incidence of birth defects (Dufour et al. 1994). Abstainers were less likely to have heard of FAS than former, current, or risk drinkers. Data from the 1990 survey revealed, however, that only 29 percent of women of childbearing age could characterize FAS correctly and that few were aware of the risks to the fetus associated with moderate levels of alcohol exposure during pregnancy. The lack of awareness among the survey respondents occurred despite the issuance of the 1981 recommendation by the Surgeon General that women abstain from drinking during pregnancy (Schydlower et al. 1993).

> *Although the overall consumption of alcohol by pregnant women appears to be declining, drinking among certain high-risk groups is unchanged.*

For all women and women who were drinkers, awareness of the harmful effects of drinking during pregnancy was significantly higher in 1990 than in 1985. Awareness did not increase significantly among African-American or Hispanic women; among women with less than 12 years of education or with lower family income; and among women who were unemployed, divorced, or separated. In fact, black women, Hispanic women, and women with family income of less than $20,000 per year were less likely than all women combined to have heard of FAS. Nonetheless, many women, particularly African Americans, still report not being counseled about the risks of drinking during pregnancy (Kogan et al. 1994).

Although the overall consumption of alcohol by pregnant women appears to be declining, drinking among certain high-risk groups, including smokers, unmarried women, African Americans, Hispanics, young drinkers (less than 30 years), and those with limited education (less than 12 years) is unchanged. This information, as well as findings from the surveys described earlier, point to a need for prevention efforts that educate the public about the specific characteristics of FAS, rather than merely attempting to increase general awareness of the syndrome. In addition, these findings emphasize the need for prevention approaches that specifically target individuals who are at high risk for poor pregnancy outcome (Cornelius et al. 1993; Serdula et al. 1991).

Screening for Risk Drinking

Given that some effects of even heavy drinking can be reversed if women reduce drinking after the first trimester, researchers have directed significant efforts at effectively identifying and intervening with women who drink alcohol while pregnant. Currently available biological markers, which detect abnormalities in body biochemistry that have been caused by excessive drinking (such as aspartate aminotransferase and gamma-glutamyltransferase), lack sensitivity and specificity thus rendering them ineffective as screening tools in clinical practice (Chan 1991). Thus, the need to screen large numbers of women for alcohol problems has prompted the development of several brief screening questionnaires. These questionnaires, namely the T-ACE (Sokol et al. 1989), the TWEAK (Russell 1994; Russell et al. 1994), the NET (Bottoms et al. 1989), and 4P's (Burke and Caldwell in press), are based on research in obstetric populations. Adapting questions from screening instruments for the general population, such as the CAGE (Ewing 1984) and the MAST (Selzer 1971), the new questionnaires have been designed to help physicians in their efforts to identify pregnant patients with an alcohol problem.

The T-ACE instrument employs three of the four questions from the CAGE: Have people ANNOYED you by criticizing your drinking? Have you ever felt you ought to CUT down on your drinking? Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (EYEOPENER)? Added to the questionnaire, however, is a question that indirectly addresses a woman's

TOLERANCE (i.e., how many drinks does it take to make you high? With an alternative question asking how many drinks the woman can hold) for alcohol. Questions about tolerance avoid triggering denial and minimizing of drinking by the respondent. Sokol et al. (1989) consider a woman to be alcohol tolerant if she requires more than two drinks to feel the effects of alcohol.

The NET instrument employs questions from the MAST (Do you consider yourself a NORMAL drinker?) and the CAGE (Do you ever have an EYEOPENER?) questionnaires as well as the tolerance question from the T-ACE. Any positive NET item is interpreted as a positive screening score.

The TWEAK also combines questions from the CAGE, MAST, and T-ACE questionnaires. This test asks the interviewee, How many drinks can you hold (TOLERANCE)? Are others WORRIED about your drinking? Do you sometimes drink when you first get up in the morning (EYEOPENER)? Has a friend told you about things that you did while you were drinking that you cannot remember (AMNESIA or blackouts)? Do you feel the need to (K) cut down on your drinking? In scoring the test, an interviewer assigns two points each to positive responses to the tolerance and worry questions and one point for a positive response to each of the remaining questions. A score of two or more indicates that a woman is likely to be a risk drinker.

Russell et al. (1994) assessed the efficacy of the TWEAK, T-ACE, NET, MAST, and CAGE in detecting periconceptional drinking among 4,743 African-American women attending an inner-city prenatal clinic. Across a range of potential cut points, the five-item TWEAK proved to be more sensitive (a measure of the degree to which an instrument is successful in identifying all the risk drinkers in a population) than the four-item T-ACE and the three-item NET, combining high sensitivity with reasonable specificity (Russell et al. 1994). Findings from this evaluation validated the utility of the T-ACE in screening for risk drinking among pregnant women and suggested that the TWEAK may "outperform" the T-ACE.

> *Alcoholic women generally appear unable to respond to educational interventions that have proved to be effective with social drinkers, probably because many deny the severity of their symptoms.*

Although the MAST (Selzer 1971) and maternal self-report continue to be useful research tools, validation of these short screening instruments supports their utility for clinical use because they are quicker to administer and easier to score. Prior administration of screening may even increase the validity of subsequent quantitative questions about intake (Russell et al. 1994; Steinweg and Worth 1993). Some women who are risk drinkers are missed by brief screening yet are detected by direct questioning about their drinking patterns (Russell 1994). In literate populations, self-administered alcohol questionnaires may be most reliable because some women may report their alcohol-related behavior more fully on the questionnaire than they would to their physicians (Chan et al. 1993; Lapham et al. 1991).

Interventions

Alcoholic women generally appear unable to respond to educational interventions that have proved to be effective with social drinkers (Smith and Coles 1991), probably because many deny the severity of their symptoms (Johnson 1986). However, supportive counseling focused on the reduction of alcohol consumption and on potential benefits to the fetus (rather than guilt-provoking criticism) has been successful even with heavy drinkers. Thus, intervention among high-risk pregnant drinkers can be an effective means of preventing FAS and ARBD (Rosett et al. 1983; Weiner et al. 1989). The most effective intervention approaches avoid the use of moral or volitional injunctions (e.g., "Just say no" or "Stop lest you harm the baby"). Emphasis on abstinence primarily for the good of the baby, however, carries two risks: feelings of disenfranchisement of the mother and high relapse rates after childbirth (Raskin 1993).

Problems co-occurring with alcohol abuse can further complicate treatment of the mother and efforts to prevent FAS and ARBD in the offspring (Haller et al. 1993; Raskin 1993). High incidence of polysubstance use, depression, anxiety, and personality disorders (most frequently antisocial, borderline, paranoid, and dependent disorders) as well as a family history of addiction, impoverished and chaotic home background, poor education, and limited intellectual functioning suggest that most traditional short-term treatments may be used, at best, to reduce drinking during a specific pregnancy (Raskin 1993). To interrupt the familial alcoholism pattern, more costly interventions designed along developmental lines may be necessary (Haller et al. 1993).

A few active prevention programs, including prenatal clinic and community-based programs or training programs for professionals, have been undertaken (e.g. Streissguth et al. 1994*c,d*), but almost no systematic studies have been conducted to evaluate which aspects of the interventions are most effective. A macrolevel approach to prevent FAS among Native American populations throughout the United States has provided local individuals and communities with comprehensive information and assistance in carrying out prevention and intervention on their own (May and Hymbaugh 1989). Individuals trained to be local trainers were successful in transmitting FAS information to prenatal groups, elementary and secondary school children, and community groups and retained knowledge themselves when tested 2 to 4 months later, despite problems of turnover and motivation among some of the trainers.

Although alcohol-abusing women may be particularly receptive to intervention strategies during pregnancy, they appear to be less likely to seek out treatment. This may be due to the stigma attached to alcoholism while pregnant or because residential programs frequently lack provisions for child care for their other children (Smith and Coles 1991). Active outreach is critical for locating women at highest risk for poor outcome, particularly because many at high risk may not use prenatal care.

Characteristics and Benefits of Animal Models

Because alcoholic women often abuse tobacco, have poor health, and are malnourished, clinical researchers initially were unable to determine whether alcohol alone produced the anomalies associated with FAS. Accordingly, researchers began to conduct animal studies to confirm alcohol's teratogenic actions on a developing fetus and to address the initial skepticism over the idea that maternal alcohol consumption during pregnancy could have such devastating effects on infants. In 1977, two laboratories (Chernoff 1977; Randall et al. 1977) reported that mice exposed to alcohol prenatally were smaller and had birth defects similar to those reported in humans with FAS. By controlling for confounding variables in the mother, such as other drug use, general health, and nutritional status, these investigators were able to verify in mice that alcohol is a teratogen. Since then, animal models of alcohol-induced birth defects have effectively advanced our understanding of the biobehavioral expression, risk factors, and mechanisms of the consequences of prenatal alcohol exposure.

Animal models and in vitro biological systems derived from animals present some significant advantages for studying the actions of alcohol on a developing fetus (Hannigan and Abel 1995). For example, such models enable researchers to conduct controlled experiments to examine how the complex pharmacologic, biochemical, and physiologic effects of alcohol are influenced by and interact with the various genetic, experiential, social, and behavioral factors that influence alcohol's effects in humans. Unlike in clinical studies, this analysis can be performed in hundreds of animals, thereby greatly increasing the power of observations. Animal models also enable researchers to control, exclude, and measure potent factors that may confound understanding of FAS and ARBD in studies of human populations. Thus, animal models are a great resource for examining how alcohol acts on a fetus, how other influences associated with alcoholism in humans (such as concurrent abuse of other drugs or poor nutrition) contribute to the adverse outcomes of prenatal exposure to alcohol, and how FAS and ARBD can be treated or prevented.

Animal and cellular studies, however, are not without limitations, which should be taken into consideration when experimental results are interpreted (Hannigan and Abel 1995). For example, researchers have yet to develop an animal model of FAS per se because offspring of pregnant animals exposed to alcohol do not display the full clinical expression of the syndrome as it occurs in humans. In addition, other animal species do not metabolize alcohol exactly as humans do, and the gestational process is not completely analogous in different species. Finally, various alcohol-related effects observed in humans, such as impairments in social behavior and higher cognitive functioning, cannot be modeled satisfactorily in nonhuman subjects.

Several well-defined animal models, however, serve as valid and effective tools for examining specific hypotheses about the risk factors, outcomes, and mechanisms of prenatal alcohol exposure. Although there is no single "ideal" model that corresponds to the human expression of FAS, each of the available model systems is effective for assessing specific aspects of alcohol's broad effects. Investigators have used whole animals, or in vivo models (e.g., rodents, sheep, tadpoles, and chicken eggs), and isolated organs or cells, or in vitro models (e.g., perfused human placenta, incubated whole mouse embryos, cardiac myocytes, developing rat nervous system, rat brain slices, and cell lines derived from human brain tumors), in their efforts to identify and characterize the effects of alcohol on the fetus. Key results from these cellular and animal models are discussed below, illustrating recent progress in our understanding of the consequences of prenatal alcohol exposure.

Critical Doses and Periods of Exposure

A fundamental question that continues to be difficult to address in human studies is, How much alcohol is too much? (see Jacobson and Jacobson 1994 for a review). Although findings from human studies have provided knowledge of critical doses, or thresholds, of alcohol, this issue continues to be an important research concern. Animal models are proving to be useful for determining threshold doses to various prenatal alcohol-related outcomes. Findings from these studies can have important implications for identifying women at risk, devising effective prevention efforts, and disseminating accurate information to the public.

Studies conducted in mice and in macaque monkeys demonstrate that early embryonic alcohol exposure (first trimester) is associated with facial and cardiac malformations similar to those reported in children with FAS.

Controlled experiments with animal models have demonstrated clearly that the peak maternal blood alcohol concentration (BAC) determines the likelihood and severity of alcohol-induced impairments in offspring exposed prenatally to alcohol (West and Goodlett 1990; West et al. 1990). This finding indicates that the total amount of absolute alcohol consumed (dose) is not the only factor that influences the outcome of offspring. The pattern of alcohol drinking also is a critical factor (Bonthius and West 1990; West 1993): Rapid drinking over a short period will result in a higher BAC than drinking the same amount of alcohol over a longer period. The demonstrated importance of peak BACs implies that estimates of average alcohol consumption used in clinical studies (e.g., drinks per day throughout pregnancy) may not be sensitive enough to determine human thresholds reliably and suggests that researchers who are involved in human studies should ask women about their pattern of drinking in addition to their total consumption (Day 1992).

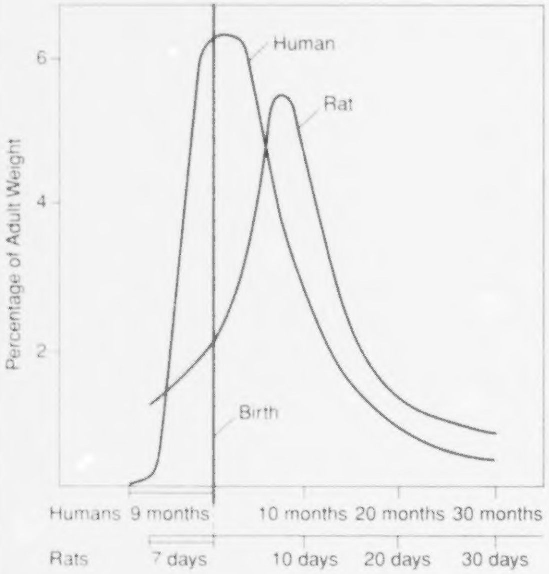
Animal studies also have demonstrated that the period(s) during pregnancy when blood alcohol levels are high has an important influence on the variable expression of birth defects associated with prenatal alcohol exposure (Becker et al. 1994; Randall 1987; Webster 1989). All developing organs are susceptible to the effects of alcohol, yet the greatest risk for damage appears to be during maturational stages when tissues and organs are growing most rapidly.

Scientists have divided the prenatal period in humans into three phases: the redifferentiation period (from conception to implantation of the fertilized egg in the uterus), the embryonic period (up to 8 weeks in pregnancy), and the fetal period (from 8 weeks to delivery). During the embryonic period, complex tissues and organs are formed, and exposure to teratogenic agents such as alcohol during this period can result in gross malformations of organ systems. Such malformations can arise due to the disruption of several embryonic events at the cellular level: cell division and proliferation, cell growth and differentiation (a process by which cells become specialized in structure and function), and cellular migration (which involves the movement of maturing cells to their ultimate locations so that they can serve a specific role in the overall coordinated activity of an organ). Each of these stages is directed by nutritional, hormonal, and cellular factors. Alcohol can influence the actions of these factors and affect organ formation and growth. During the fetal period, exposure to alcohol generally does not cause gross structural malformations but can produce subtle damage to the CNS and other organ systems. Early alcohol exposure in animals also has been associated with spontaneous abortion (Clarren and Astley 1992).

Studies conducted in mice (Sulik and Johnston 1983) and in macaque monkeys (Clarren et al. 1988) demonstrate that early embryonic alcohol exposure (first trimester) is associated with facial and cardiac malformations similar to those reported in children with FAS. Craniofacial anomalies are of particular interest because they are used for FAS diagnosis and appear to indicate brain abnormalities (discussed later) (Kotch and Sulik 1992*b*).

Figure 5. Timing of the brain growth spurt during development in humans and rats.

In the rat (scale is measured in days), the brain's growth peaks *after* birth, whereas in humans (scale is measured in months), the brain's growth peaks *at* birth. Growth is measured as a percentage of adult weight. As brain growth slows, continued growth in the rest of the body causes the brain's weight to become a smaller percentage of total adult weight.



Source: Modified from Dobbing 1981.

The brain is one of the first organ systems to begin to develop and the last to be completed. It is not surprising therefore that the CNS appears to be sensitive to the adverse effects of alcohol throughout development in humans and in animals (Coles 1992, 1994; West and Goodlett 1990). Clarren et al. (1988) observed that monkeys exposed to alcohol early in gestation displayed neurobehavioral effects; such effects occurred even in the absence of obvious physical defects. Alcohol exposure later in gestation also can disrupt brain development. Miller (1992) noted that brain weights were diminished in rats exposed to alcohol during the second half of gestation (equivalent to the second trimester in humans). Normally, nerve cells are generated in the *neocortex* during this period of development and then migrate to appropriate sites throughout the brain. Alcohol exposure appears to affect the timing and pattern of nerve cell generation. It also appears to change cellular migration patterns, producing unusual cell formations in such regions of the brain as the neocortex, hippocampus, cerebellum, and *sensory nucleus* (Miller 1992) (see figure 1). Scientists assume that misplaced cell formations are not fulfilling their normal roles within the brain and may contribute to the impairments of FAS.

The effects of alcohol exposure during the third trimester are of particular interest to researchers because the brain growth spurt—a time of rapid brain development—occurs within this period of development in humans (figure 5). Using a rat model, West and Goodlett (1990) examined the effects of alcohol exposure during the early postnatal period, the period of gestation in rats that corresponds to the third trimester of pregnancy in humans. Alcohol exposure during this developmental period led to reductions in brain weight and head circumference, which likely were associated with changes in brain structures and functions. Cell numbers in certain parts of the hippocampus and the cerebellum also were reduced (Hamre and West 1993). Such anatomical changes seemingly have a behavioral effect later in life: Rats exposed to alcohol during this developmental period were hyperactive and had learning deficits (West and Goodlett 1990).

Abdollah et al. (1993) noted that alcohol also had a dose-dependent effect on hippocampal development in prenatally exposed guinea pigs. Pups born to mothers that were treated chronically with selected doses of alcohol displayed hippocampal injury and behavioral dysfunction. These findings are interesting because prenatal brain development is more extensive in the guinea pig than in the rat.

Alcohol also appears to have concentration and time-dependent effects on neural tube formation. Hunter et al. (1994) exposed 9-day-old mouse embryos in vitro to several concentrations (300, 450, 600, and 800 mg/dL) of alcohol. Embryos exposed to higher concentrations showed neural tube defects after 8 hours, whereas embryos exposed to lower concentrations required 20 hours of exposure to show defects. After 24 hours, neural tube defects were evident in all embryos treated with higher doses and in 20 percent of those treated with lower doses of alcohol. The investigators concluded that alcohol-induced neural tube defects are a function of the duration and concentration of alcohol exposure.

The regional selectivity of alcohol-induced CNS malformations is evident in children with FAS and in animal models. Derivatives of the neural crest, for example, appear to be particularly sensitive to exposure early in gestation (e.g., Carones et al. 1992; Davis et al. 1990; Kotch and Sulik 1994*a*), including the face, corneal endothelium, and heart.

Findings from animal studies suggest that some brain regions are more sensitive than others to alcohol's teratogenic actions. Also, some cell populations within the brain are more vulnerable than others to alcohol's effects, even within a particular brain region (West 1986). Types of cells within the CNS, such as cholinergic neurons and neural crest cells, appear to be more sensitive to alcohol at certain stages (Brodie and Vernadakis 1990; Davis et al. 1990) or even on single days during development (Rahman et al. 1994). How prenatal alcohol exposure, neonatal alcohol exposure, or both affects cellular organization of each brain area depends on when populations of neurons, or nerve cells, in the specific brain regions proliferate, migrate, and differentiate (see Miller 1992 for a review).

> *Among the diagnostic features of FAS in humans, reduced fetal growth or birth weight is perhaps the most reliably demonstrated feature in animals.*

Consequences of Prenatal Alcohol Exposure in Animals

The biological and neurobehavioral consequences of prenatal alcohol exposure in animals (mostly rodents but including nonhuman primates) remain remarkably consonant with effects in humans (Driscoll et al. 1990). This consonance with clinical FAS has been recognized for years (see Abel 1984, Becker et al. 1994, Hanningan et al. 1992, Meyer and Riley 1986, and Randall 1987 for reviews) and has helped to validate animal models of the syndrome; to specify that particular outcomes are due to alcohol itself; and to point to additional problems, such as auditory-processing deficits (Church 1987; Church et al. 1987; Church and Gerkin 1988), that may be found in humans. In general, findings from animal studies indicate that the fundamental effects of prenatal alcohol exposure are poor overall growth, malformation of major organs, craniofacial anomalies, and various degrees of CNS dysfunction. The following discussion of selected studies will illustrate the progress that has been made in identifying and understanding the actions of alcohol on a developing fetus.

Growth and Physical Effects

Among the diagnostic features of FAS in humans, reduced fetal growth or birth weight is perhaps the most reliably demonstrated feature in animals (Hannigan et al. 1993). Low birth weight in humans can be caused by many prenatal factors, yet the systematic occurrence of growth retardation in animals exposed prenatally to alcohol provides evidence that alcohol impairs growth. Alcohol-exposed offspring typically remain smaller than control animals, although catchup growth is possible in some instances as animals mature (Becker et al. 1994). According to a recent study (Guo et al. 1994), persistent growth retardation may be due, in part, to poor nutrient absorption that results from the injurious effect of alcohol on the mucosal lining of the fetal small intestine.

As noted earlier, alcohol dose, peak BAC, and timing of alcohol exposure during gestation can influence the severity and duration of fetal growth retardation (West and Goodlett 1990). Postnatal factors also appear to come into play. In fostering experiments, the severity of various deficits in alcohol-exposed rats lessened when alcohol-affected pups were nursed and raised by dams who did not receive alcohol (Abel 1984; Vorhees 1989).

Low birth weight can be nonspecific in origin and the expression of CNS dysfunction variable in infants. The co-occurrence of the characteristic facial features associated with prenatal alcohol exposure thus can be essential to diagnosing FAS in humans (Aase 1994; Sokol and Clarren 1989). In alcohol-exposed experimental animals, the general dysmorphic patterns of facial features appear to resemble those in children with FAS (Aase 1994; Escobar et al. 1993). One mouse strain is particularly vulnerable to developing the patterns of midface underdevelopment and short eye openings (Kotch and Sulik 1992*b*); these features also are seen in monkeys (Astley et al. 1992; Clarren et al. 1988) and have been detected radiographically in rats (Edwards and Dow-Edwards 1991).

Understanding how alcohol produces craniofacial anomalies is an important research question, particularly in light of recent evidence that such facial defects are associated with brain malformations (Kotch and Sulik 1992*b*; Siebert et al. 1990, 1991). Fadel and Persaud (1992) noted that alcohol delayed the maturation of craniofacial areas in mouse embryos. Kotch and Sulik

(1992*a*) found that exposure to alcohol on different gestational days had specific teratogenic effects on facial development in mouse embryos; such effects were caused by excessive cell loss along the rim of the anterior *neural fold* (Kotch and Sulik 1992*a*).

Alcohol's selective toxic effect on early embryonic neural crest cells also may play a role in facial anomalies. Neural crest cells migrate through peripheral tissue and give rise to several types of neurons in the peripheral nervous system, including neurons and glial cells in cranial and spinal sensory as well as autonomic ganglia, different types of connective tissue, and Schwann cells (specialized glia) of peripheral nerves. Davis et al. (1990) observed that neural crest cells in cultured chick were sensitive to the effects of alcohol. Alcohol also inhibited *DNA* and protein synthesis, and thus cell growth, in embryonic palate cells from certain mouse strains (Weston et al. 1994).

Anomalies in major organs and skeletal structure, long recognized as consequences of fetal alcohol exposure in humans (see Abel 1990 and Majewski 1981 for reviews), are also common in animal models. For example, both humans and mice exhibit similar patterns of skeletal defects. Mice can have incomplete growth of forelimbs and fused, misshapen, or missing digits or ribs (Kotch et al. 1992; Weinberg et al. 1990). Gastrointestinal (Guo et al. 1994) and urogenital anomalies also are seen in both experimental animals and humans (Randall 1987; Taylor et al. 1994*b*), as are cardiac malformations. Developmental delay in the maturation of the heart (Fadel and Persaud 1992), defects in the wall of the ventricular chamber of the heart (see Abel 1990), and malformations in the vasculature of the heart (see Becker et al. 1994) have been found in mice and children. A potential contributor to alcohol's disruptive actions on fetal heart development is decreased DNA and protein synthesis during the periods of fastest growth of cardiac tissue, an effect observed when alcohol is added to cell cultures of cardiac cells (Adickes et al. 1993).

Behavioral and Cognitive Abnormalities

As detailed earlier, increasingly sophisticated psychological assessment approaches have provided evidence of persistent cognitive, attentional, and neurobehavioral abnormalities in children with FAS and ARBD (Jacobson and Jacobson 1994). Longitudinal study populations of humans with FAS are still young, and researchers are only beginning to discover how the behavioral and physical problems of FAS and related disorders are manifested in adults. Given that animals mature significantly faster than humans do, animal studies have offered the opportunity to examine the long-term effects of prenatal alcohol exposure in a relatively shorter period than would be possible in humans. Through animal studies, researchers have addressed how in utero alcohol exposure affects lifelong behavioral and cognitive functioning.

Animals exposed prenatally to alcohol exhibit such neurobehavioral problems as hyperactivity, perseveration,[4] poor balance and coordination, difficulty walking, and inability to learn from past experiences (Becker et al. 1994; Riley et al. 1979). Studies using rodent models have helped to elaborate the nature of age-dependent behavioral hyperactivity and learning deficits (see Meyer and Riley 1986*b*), problems that also are associated with fetal alcohol exposure in humans. For example, Catlin et al. (1993) noted that guinea pigs exposed prenatally to alcohol exhibited a dose-dependent hyperactivity that persisted into adulthood. Rats displayed disruptions in spatial and temporal-pattern learning and memory (Goodlett et al. 1992; La Fiette et al. 1994). Performance deficits in these animals have been characterized as memory (Greene et al. 1992) or spatial-processing impairments (Goodlett et al. 1992) rather than as failures to use sensory cues in their environment.

To test the effect of alcohol on memory and spatial-learning performance, Hall et al. (1994) trained rats exposed prenatally to alcohol to perform in a radial arm maze. The rats had difficulty learning to perform, which indicated a problem with spatial learning. Older alcohol-affected rats with prior experience in the maze, however, seemingly remembered how to perform when retested. Therefore, it appears that once the animals acquired the ability to perform in the radial arm maze, they retained the ability into adulthood.

Dumas and Rabe (1994), however, reported that a single in utero episode of high-peak BACs in mice produced a modest deficit in memory retrieval in young adults and a profound deficit in older (2-year-old) adults;

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[4] This neurobehavioral problem is defined as the repetition of a mental activity with an inability to switch to another activity. In animals, it can be measured through observing various behaviors, such as an alcohol-exposed animal's reduced ability to choose a goal other than the one initially chosen in a trial setting.

young (3-month-old) mice showed no evidence of problems with memory retrieval. Similar results were reported by Minetti et al. (1996). These studies suggest that functional deficits stemming from embryonic exposure to alcohol may interact with those of aging to cause an early emergence of age-related memory problems. They also provide additional evidence of the persistent effects of prenatal alcohol exposure in animals reported earlier (Riley 1990).

Some investigators have observed that animals exposed prenatally to alcohol have differential reactivity or tolerance to alcohol (Reyes et al. 1993*a*). The observed tolerance may be influenced by functional changes in the neurotransmitter dopamine (Becker et al. 1993; Blanchard et al. 1993). Alternatively, because of in utero experience with alcohol, rat fetuses may become familiar with or develop learned associations with the sensory qualities of alcohol in the amniotic fluid. Prenatal experience with alcohol can influence postnatal responses to alcohol and may influence processes associated with the initiation of alcohol intake in rats (Chotro et al. 1991; Chotro and Molina 1992; Dominguez et al. 1993). Scientists have yet to determine whether fetal alcohol exposure can influence behavioral sensitization to alcohol (Hunt and Lands 1992) or the development of alcoholism in humans.

Damage to the cerebellum may account for motor coordination problems, such as muscle tremors, impaired gross and fine motor function, and balance and gait deficits, that can occur in children and animals affected by prenatal alcohol exposure.

Neuroanatomical Outcomes

Normal brain development depends on sequential patterns of gene expression, cell proliferation and differentiation, neuronal migration, and formation of connections between neurons, called synapses.

Prenatal alcohol exposure can produce various structural changes in the fetal CNS by altering any of these steps. The specific changes that develop depend on dose, duration, and pattern of alcohol exposure as well as on the critical developmental periods during which exposure occurs (Miller 1992, 1993; Miller and Al-Rabiai 1994; Pentney and Miller 1992). For example, several researchers noted that neonatal alcohol exposure during differentiation of cerebellar Purkinje cells (cells responsible for carrying information out of the cerebellar cortex) in rats caused significant loss of these cells and reduced expression of messenger RNA (mRNA) for myelin basic protein. Exposure to equivalent doses during Purkinje cell formation, however, did not affect cell numbers (Marcussen et al. 1994; Zoeller et al. 1994). Damage to the cerebellum may account for motor coordination problems, such as muscle tremors, impaired gross and fine motor function, and balance and gait deficits, that can occur in children and animals affected by prenatal alcohol exposure.

Recent research suggests that the effect of alcohol on the cell-cell adhesion molecule L1 may play a role in FAS and FAE (Ramanathan et al. 1996). Cell adhesion molecules influence the ability of cells to migrate, sort themselves out, and stabilize spatial relationships considered important for cell differentiation. Mutations in the gene for L1 produce mental retardation and various brain malformations also seen with prenatal alcohol exposure (Wong et al. 1995). Thus, researchers questioned whether FAS arises partly through alcohol's effects on L1-mediated cell-cell interactions. Ramanathan et al. (1996) observed significant inhibition of cell-cell adhesion at BACs as low as 1 millimolar, which is less than the blood alcohol level achieved after ingesting one alcoholic beverage. The findings establish that human L1 is a sensitive and specific target of alcohol.

Sensory Systems

In animals and humans, prenatal exposure to alcohol causes auditory and visual defects. Children with FAS have a high prevalence of hearing impairment resulting from structural damage to the ear. These children also commonly have problems with visual processes, producing impaired visual acuity and nearsightedness. Evidence suggests that these abnormalities may result from the toxic effects of alcohol on neural crest cells, which give rise to sensory neurons (Carones et al. 1992). Thus, the developing sensory systems of the CNS appear to be vulnerable to the effects of alcohol (Miller and Dow-Edwards 1993).

Animals exposed in utero to alcohol experience hearing loss and develop a pattern of eye anomalies similar to those seen in humans. Studies in mice have shown that early prenatal alcohol exposure causes cell death at embryonic sites that correspond to cell populations forming the sensory cells of the inner ear (Kotch and Sulik 1992*a,b*). Congenital hearing loss in rats exposed prenatally to alcohol has been associated with a central auditory processing disorder and with lesions and malformed cilia (hairlike projections) on auditory sensory receptor cells (Church et al. 1996).

Investigations of the possible causes underlying visual deficits have revealed that fetal alcohol exposure in rats and mice reduces the number of *axons* and the proportion of myelinated (insulated) axons (Ashwell and Zhang 1994) in the optic nerve (which connects the eye to the brain)(Ashwell and Zhang 1994; Strömland and Pinazo-Duran 1994). Changes in the optic nerve may reflect direct effects of alcohol on the retina late in gestation (Ashwell and Zhang 1994; Fadel and Persaud 1992; Strömland and Pinazo-Duran 1994). Furthermore, reduced optic nerve myelination may be due, in part, to delayed maturation of oligodendrocytes (small glial cells [discussed below] that contribute the myelin sheath to the axon) (Phillips and Krueger 1992). Evidence from animal studies thus suggests that the visual system abnormalities seen in FAS children are due directly to the effects of alcohol (Carones et al. 1992; Strömland and Pinazo-Duran 1994).

Glia

Glial cells are "nonneural" cells in the brain that participate in a variety of normal functions. Oligodendrocytes are special glial cells that form myelin around axons in the CNS. Another type of glial cell, known as astrocytes, fulfills several functions, such as structural support for nerve cells, proliferation and repair after injury to nerves, and isolation and grouping of nerve fibers and terminals; their interaction with neurons is of the utmost importance in the developing CNS. A special kind of glial cell, known as radial glia, appears only during embryonic development and guides migrating neurons; after neurogenesis, these cells are transformed into astrocytes. Neuronal migration is the basis of the CNS pattern for regional specificity.

> *Evidence from animal studies thus suggests that the visual system abnormalities seen in FAS children are due directly to the effects of alcohol.*

Growing awareness of the importance of radial glia and other types of astrocytes in neuronal development has led scientists to question whether alcohol affects astrocytes and whether such effects may have a role in the developmental injuries associated with FAS. Studies indicate that alcohol disrupts myelination and the maturation of astrocytes and other glial cells (Lancaster 1994); such alcohol-related changes may contribute to the brain defects associated with prenatal alcohol exposure (Fletcher et al. 1994; Ledig and Tholey 1994; Phillips 1994).

Expression of glial fibrillary acidic protein, a marker of astrocyte development, often is used experimentally to characterize the response of developing glial cells to alcohol. Alcohol-induced changes in expression of this protein may vary in specific brain regions and with timing of alcohol exposure relative to particular stages of astrocyte differentiation. For example, some evidence suggests that prolonged exposure to alcohol during gestation in the rat reduces the protein's expression in Bergmann glia, the radial glia in the cerebellum (Shetty and Phillips 1992). In the cerebral cortex of the brain, however, expression of the protein increases after prenatal exposure to alcohol (Miller and Robertson 1993). In addition, binge-like exposure during the postnatal brain growth spurt in rats (a period that corresponds to the third trimester of pregnancy in humans) has been shown to increase glial fibrillary acidic protein mRNA in the cerebral cortex (Fletcher and Shain 1993, 1994). These results suggest that alcohol may delay the maturation of Bergmann glia in the cerebellum and prematurely accelerate conversion of radial glia to astrocytes in the cerebral cortex (Miller and Robertson 1993). Such effects could disrupt the migration of neurons guided by Bergmann and radial glia, producing the misplacement of neurons that is seen in FAS (Miller 1993).

Neurochemistry

Neurotransmitters, hormones, and growth factors, as well as the cascade of intracellular signal transduction processes (i.e., second messenger systems) they initiate, are altered by alcohol exposure in utero (Druse 1992; Pennington 1992). It can be difficult to generalize about the effects of alcohol on neurochemical factors because studies have produced a variety of findings. However, studies have shown that perinatal alcohol exposure (i.e., shortly before or after birth) in animals does appear to affect serotonin, dopamine, acetylcholine, glutamate, and gamma-aminobutyric acid (GABA) neurotransmitter systems (Druse 1992)(see Chapter 3, Actions of Alcohol on the Brain).

The nature of alcohol's effect on neurotransmitter dysfunction may depend critically on when alcohol exposure occurs. For example, Kentroti and Vernadakis (1992) observed that early embryonic exposure in chicks appeared to shift the phenotypic expression of neuroblasts from cholinergic to γ-GABA neurons. Cholinergic neuronal cells may be more sensitive to early exposure to alcohol and GABA neurons to later exposure. Alterations in brain chemistry may account for the behavioral dysfunction in FAS, and one day these alterations may be ameliorated by drugs acting on affected neurochemical systems (Hannigan and Blanchard 1988).

In recent years, neurochemistry studies have focused on the influence of in utero alcohol exposure on monoamine neurotransmitters (i.e., dopamine and serotonin). Prenatal exposure to alcohol markedly affects the development of the dopamine system. Druse (1992) observed that dopamine and its metabolite levels were reduced in alcohol-exposed fetal and young rat brains, although these changes may not always persist into adulthood (Middaugh et al. 1994). In addition, animals exposed prenatally to alcohol display altered behavioral responses to drugs that act on the dopamine system, an outcome that indicates that dopamine function in the two principal dopaminergic fiber systems in the brain—the mesolimbic and nigrostriatal systems—is affected (Becker et al. 1993; Hannigan and Pilati 1991). Such exposure also has been shown to alter activity of dopamine neurons in the substantia nigra (the layer of gray matter that separates the anterior and posterior portions of the midbrain) (Shen and Chiodo 1993) and midbrain (Shen and Chiodo 1993; Shen et al. 1995) but seemingly does not affect concentration of G proteins associated with dopamine receptors (Druse et al. 1994). Many of these effects are consistent with morphological indices of delayed dopamine neuron maturation and aberrant dendritic growth and organization in the substantia nigra, which is rich in dopamine and appears to play a role in the addictive effects of alcohol and other drugs of abuse (Shetty et al. 1993). Given the role of dopamine in a variety of neurobehavioral events, such as feeding, motor activity, and arousal (all of which can be impaired in offspring exposed prenatally to alcohol), these effects on the developing dopamine system may play a role in neurobehavioral deficits.

Experimental evidence has shown that maternal drinking also affects fetal serotonin levels. In a study by Druse et al. (1991), exposure to high levels of alcohol reduced levels of serotonin, its metabolites, and the serotonin 5-HT_{1A} receptor binding sites by 40 to 60 percent in some brain areas (primarily the neocortex and cerebellum) but not in others (e.g., the hippocampus, hypothalamus, and striatum). Lokhorst and Druse (1993*a*) also observed that alcohol reduced serotonin uptake into astrocytes (Lokhorst and Druse 1993*a*), although there were no changes in several measures of serotonin function when alcohol was added to cultured serotonin neurons (Lokhorst and Druse 1993*b*). The effects of prenatal alcohol exposure on serotonin are important because this neurotransmitter is thought to play an important role in neuronal maturation and differentiation during embryonic development and is implicated in a variety of neurobehavioral functions (Lankford et al. 1988; Lauder et al. 1983).

Changes in other neurotransmitters also have been related to behavioral problems. For example, deficits in the performance by mice in the radial arm maze were associated with increases in the density of muscarinic receptors (which bind the neurotransmitter acetylcholine) in the hippocampus of neonatal mice given daily injections of alcohol for 2 weeks (Pick et al. 1993). The hippocampus is important for learning, especially of information that requires constant updating. Prenatal alcohol exposure in rats, however, did not produce significant changes in hippocampal muscarinic receptors (Weinberg and Petersen 1991; Wigal et al. 1990), although the signal transduction process associated with activation of the receptor may be reduced (Reno et al. 1994; Tan et al. 1993).

The influence of acute and chronic exposure on glutamate and the *N*-methyl-D-aspartate (NMDA) receptor that binds glutamate also has received considerable attention. Glutamate is the major excitatory transmitter in the mammalian CNS, and its function in the fetal brain may be more sensitive to alcohol than in the adult brain. Reynolds and Brien (1994) noted that alcohol administration depressed glutamate release from the hippocampus in fetal guinea pigs but not in adults, and immature fetuses were more sensitive to this effect than mature fetuses. Alcohol also inhibited NMDA receptor-mediated excitotoxicity in cultured fetal neuronal cells (Chandler et al. 1993) and curbed NMDA receptor-mediated ion channel function in neuron cultures (Lee et al. 1994), possibly by altering the structural properties of the ion channel. Scheetz and Constantine-Patton (1994) have proposed that the vertebrate nervous system has evolved a mechanism for regulating the NMDA receptor function to solve the problem of dramatic changes in excitation in development.

Neuroendocrine Dysfunction

In addition to CNS neurochemical alterations, prenatal alcohol exposure in rats produces long-lasting hormonal changes (McGivern and Riley 1993; Weinberg 1993). The production and release of hormones from both maternal and fetal glands and from the placenta influence the formation and development of tissues as diverse as the brain and the palate (Michaelis and Michaelis 1994). Thus, altered function and balance of hormones in the fetus or in the mother can influence normal fetal development. Recent studies have begun to focus attention on the effects of maternal alcohol consumption on the endocrine function of the pregnant female and of the offspring.

Hypothalamic-Pituitary-Adrenocortical Axis

The body responds to stressful situations with certain physiologic and behavioral events. For example, stress causes the hypothalamus and pituitary gland to activate the adrenal cortex, which in turn releases corticosteroid hormones. Weinberg et al. (1986) noted that alcohol consumption during pregnancy has profound effects on the maternal and fetal hypothalamic-pituitary-adrenocortical (HPA) axis; these effects have been demonstrated under stressful and nonstressful conditions. Changes along the HPA axis range from altered corticotropin-releasing factor gene expression to altered sensitivity of the adrenal gland (Lee and Rivier 1993; Redei et al. 1993; Rivier 1993).

Changes along the HPA axis range from altered corticotropin-releasing factor gene expression to altered sensitivity of the adrenal gland.

Taylor et al. (1982) demonstrated that experimental animals exposed in utero to alcohol had reduced concentrations of corticosteroid hormones in the blood and brain during the newborn period. These hormones regulate various aspects of metabolism and influence an organism's response to stress. Corticosteroid hormone deficiency in rats exposed prenatally to alcohol led to a blunted response by the animals to several stressors (Weinberg 1989). Although this reduced responsiveness was transient (stress response normalized in the second week of life), disturbances in basal and stress-related HPA activity early in life may produce long-term effects on the animals' responses to stress in adulthood.

Hypothalamic-Pituitary-Gonadal Axis

Prenatal alcohol exposure appears to have effects at all levels of the hypothalamic-pituitary-gonadal (HPG) axis in males and females, and many of these effects persist into adulthood. In utero exposure in males can adversely affect fetal testes morphologically and hormonally (McGivern et al. 1988). Prenatal alcohol exposure also alters circulating levels of testosterone at perinatal periods in the rat, when testosterone surges are critical to organizing gender-specific brain structures (McGivern et al. 1993), and the impact of altered sex hormones may persist (Lee and Rivier 1994; Scott et al. 1992). For example, researchers have reported that the prostate, testes, and seminal vesicles are reduced in adult male rats that were exposed to alcohol before birth (Handa et al. 1985; Parker et al. 1984; Udani et al. 1985). In addition, observed changes in luteinizing-hormone secretion in exposed animals suggest a central dysregulation of the system (Handa et al. 1985). Finally, alcohol-affected males exhibit demasculinization of sexual behavior and certain brain structures (Barron et al. 1988; Parker et al. 1984; Zimmerberg and Mickus 1990) and feminization in patterns of maze learning (McGivern et al. 1984), saccharin preference (McGivern 1987; McGivern et al. 1984), and play behavior (Meyer and Riley 1986*a*). Thus, although alcohol-induced changes in sex hormones may be transient, the ultimate effects may be permanent because the exposure occurred during the critical period for sexual differentiation in the brain.

Both clinical and experimental evidence suggests that maternal drinking during pregnancy delays sexual maturation of female offspring. In an early clinical case study, Robe et al. (1980) reported that heavy maternal drinking delayed the onset of the daughter's first menstrual period. Streissguth et al. (1991) also observed delayed sexual maturation in alcohol-affected adolescent girls. These finding are consistent with findings from animal studies that show delayed vaginal opening in animals exposed prenatally to alcohol (Esquifino et al. 1986). Plasma hormone levels also are affected in female offspring: Researchers have detected increased prolactin levels and decreased luteinizing-hormone levels in newborn animals, with elevated prolactin levels persisting into adulthood (Esquifino et al. 1986). As with males, in utero alcohol exposure also appears to influence various sexual behaviors in females. Female animals show a masculine pattern of maze-learning performance, saccharin consumption, and play behavior as well as impaired maternal behavior (Barron and Riley 1990; McGivern et al. 1984; Meyer and Riley 1986*a*).

Hypothalamic-Pituitary-Thyroid Axis

Animal and human studies have shown that maternal drinking alters thyroid function in animal and human offspring (Hannigan and Bellisario 1990; Hernandez et al. 1992). Thyroid hormone deficiences may have a harmful effect on the development of some tissues, particularly the brain, because thyroid hormones are critical for normal maturation of cells in the brain and throughout the body. The impaired regulation of growth, differentiation, and general metabolic activity caused by thyroid hormone deficiencies may represent a potential mechanism by which alcohol produces its teratogenic effects. A study by Gottesfeld and Silverman (1990) offers support for the role of thyroid dysfunction in alcohol-induced injury. The investigators found that treating alcohol-affected rats with the T_3 thyroid hormone during the early postnatal period reversed physical and neuromotor developmental delays that were observed in untreated alcohol-affected animals. These data have important implications for understanding and possibly treating developmental delays in children born to drinking mothers.

> *The impaired regulation of growth, differentiation, and general metabolic activity caused by thyroid hormone deficiencies may represent a potential mechanism by which alcohol produces its teratogenic effects.*

Effects on the Immune System

In animal studies, fetal alcohol exposure has been shown to alter the immune function of offspring, making them more susceptible to infections (Giberson and Weinberg 1992; Yirmiya et al. 1993) and less responsive to mitogens (chemicals that are used experimentally to stimulate the immune system) (Wolcott et al. 1995). For example, offspring of alcohol-treated rats have reduced numbers of T lymphocytes (Weinberg and Jerrells 1991), transient reductions in B lymphocytes (Wolcott et al. 1995), and reduced immune system responses to infectious agents (Chang et al. 1994; Norman et al. 1989). In utero alcohol exposure also alters T-lymphocyte responses to infections in primates (Grossmann et al. 1993).

The immune system is responsive to and communicates with the endocrine and nervous systems (Felten et al. 1987; Grossman 1985). This regulatory circuit involving these three systems enables the body to maintain homeostasis (internal stability in response to environmental changes) more efficiently than if the systems operated separately (Giberson and Weinberg 1992). Alcohol may disrupt the development of the immune system directly, by acting on immune cells, or indirectly, by interfering with neuroendocrine systems or components of the sympathetic nervous system that are involved in immune regulation.

The sympathetic nervous system plays an important role in regulating immune responses (Felten et al. 1987). Researchers have considered whether prenatal alcohol exposure may interfere with normal immune function by altering sympathetic nervous innervation of lymphoid organs, a major source of cells of the immune system where lymphocytes develop and congregate. Studies suggest that the influence of alcohol on development of the sympathetic nervous system reduces levels of the neurotransmitter norepinephrine and beta-adrenoreceptors in the lymphoid organs (Gottesfeld et al. 1990*b*) and alters synaptic transmission in the spleen and thymus (Gottesfeld et al. 1990*a*)—all of which may affect immune response. Because these changes were observed in spleen and thymus tissue but not in heart tissue suggests that the neurochemical effects are organ specific and not related to a generalized effect of alcohol on the sympathetic nervous system.

Because of the link between the neuroendocrine and immune systems, researchers have begun to examine whether alcohol may disturb immune function through effects on hormonal actions. Several investigators have reported that fetal alcohol exposure can blunt an interleukin-induced release of HPT axis peptides that are important mediators of responses to stress and pathogens (Chang et al. 1994; Lee and Rivier 1993; Redei et al. 1993)(see Chapter 5, Effects of Alcohol on Health and Body Systems, for a discussion of the immune system). Interference with the interleukin receptor mechanisms may contribute to reduced T-cell proliferation after prenatal alcohol exposure (Chang et al. 1994). Hormones of the HPA system also may be associated with alcohol-induced dysregulation of the immune system. At birth, animals exposed to alcohol in utero have elevated levels of the hormone corticosterone in the blood and brain, elevated levels of beta-endorphin in the blood, and reduced amounts of beta-endorphin in the pituitary gland (Angelogianni and Gianoulakis 1991; Taylor et al. 1986; Weinberg 1989). They also display transient suppressed responses of beta-endorphin and the pituitary and adrenal glands to stresses (Angelogianni and Gianoulakis 1989; Taylor et al. 1986; Weinberg 1989). After weaning, however, responses of the pituitary-adrenal system and beta-endorphin to certain stressors and to such drugs as alcohol and morphine increase in these animals (Lee et al. 1990; Weinberg 1988). Prolonged elevations of HPA hormones can lead to immunosuppression and altered metabolism and thus could affect health and survival (Munck et al. 1984). It is important to note, however, that the effects of stress on immune function are complex and more research is needed to characterize the complete influence of HPA-axis activity on immunocompetence.

Maternal drinking may alter immunocompetence by depriving offspring of normal levels of maternal immunoglobin and cytokine transfer through breast milk (Giberson and Weinberg 1992; Na and Seelig 1994; Steven et al. 1993). Giberson and Blakley (1994) showed that mice exposed to alcohol in breast milk exhibited poorer immune function than mice exposed prenatally. In mice exposed to alcohol prenatally but fostered by untreated dams, immune response to mitogens returned to normal 4 to 5 weeks after birth (Wolcott et al. 1995). Drugs that stimulate the immune system may mitigate some of the effects of lactational alcohol exposure on pup immune function (Steven et al. 1993).

In summary, these studies indicate that prenatal alcohol exposure can produce long-lasting immune deficiency. The harmful effects of alcohol on the developing immune system may occur through direct effects on immune cells or through indirect effects on neural activity and endocrine function.

Basic Research on Potential Risk Factors

Little is known about why only some infants born to frankly alcoholic women have FAS, and currently clinicians and researchers cannot predict which infants will develop FAS (see Aase 1994 and Abel and Hannigan 1995). Basic research can be instrumental in advancing knowledge of risk for FAS and related problems by offering researchers experimental control and measurement precision in studies, as well as enabling them to systematically manipulate potential risk factors to directly assess their role in alcohol's effects on the fetus. Toward this end, scientists are examining the roles that genetic factors, paternal drinking, and fetal undernutrition may play in the occurrence of FAS and FAE.

Genetic Predisposition

Although it has been argued that social, behavioral, and environmental factors may be predictive of risk (Abel and Hannigan 1995; Russell 1991), the fact that FAS tends to occur more frequently in families and in certain groups has stimulated research to identify gene-based characteristics associated with teratogenic vulnerability in animals. For example, sensitivity to alcohol may influence the severity of alcohol's effects on the fetus. Gilliam et al. (1989, 1990) tested this hypothesis in long-sleep (LS) mice and short-sleep (SS) mice, which are bred for differences in response to alcohol's sedative effects. After alcohol administration, LS mice, which are more sensitive to the sedative effects of alcohol, produced litters with lower birth weight, poorer survival, and poorer learning than the relatively alcohol-insensitive SS mice given equivalent levels of alcohol. In the same study, B6 mice (included to confirm the teratogenic effects of alcohol) showed more alcohol teratogenicity than either LS or SS mice with equivalent maternal blood alcohol levels. These findings suggest that sensitivity to alcohol influences the severity of prenatal alcohol effects, yet genetic variations other than sensitivity also may contribute to increased risk for FAS and FAE.

Response to alcohol is another characteristic that has been examined for genetic association with FAS and ARBD. Researchers have selectively bred rats for a high preference (P) and a low preference (NP) for voluntary alcohol consumption; these rats also differ in their tolerance and sensitivity to alcohol. Riley et al. (1993) noted that young weanling P rats exposed to alcohol during the period corresponding to the third trimester of human pregnancy displayed greater overactivity than weanling NP rats. The finding suggests that differences in response to alcohol may be a predictor for some behavioral teratogenic effects of alcohol. The difference between P and NP locomotor activity did not persist into adulthood (Melcer et al. 1994, 1995).

Thus, animal models provide a valuable means to assess gene-based hypotheses of sensitivity to alcohol teratogenesis. To date, however, there is little evidence from clinical or basic/animal research for any particular phenotype (or genotype) related to a heritable sensitivity to FAS per se.

Paternal Alcoholism

The potential contributions of the father's drinking to the expression of FAS or FAE is a somewhat underexplored issue in research (Abel 1992; Cicero 1994). Scientists recognize that social factors accompanying the tendency of alcoholic women to consort with men who are also alcoholic can increase alcohol intake and change drinking patterns. Animal models suggest, however, that paternal drinking can contribute biologically to fetal outcome in the absence of such social factors or mate selection (Cicero 1994). Investigators have found that alcohol influences male sexual performance and fertility, viability of offspring, and maturation of the fetus and newborn (see Abel 1992 for a review). Paternal effects in animals are independent of possible genetic factors affecting fetal sensitivity to alcohol and are not general deficits mediated by poor sexual maturation after prepubertal alcohol exposure in males (Cicero et al. 1994).

Differences in response to alcohol may be a predictor for some behavioral teratogenic effects of alcohol.

Some research findings suggest that paternal alcohol ingestion before mating may have direct harmful effects on offspring. For example, Cicero (1994) found that the male offspring of male rats exposed to alcohol before mating exhibited endocrine dysfunction (e.g., lower levels of testosterone and beta-endorphin), poor spatial learning, and impaired immune function (Abel 1992; Cicero 1994). Female offspring had abnormal baseline levels of certain stress-related hormones and responded differently to stress than did control offspring. Although the mechanisms responsible for these deficits are not explained easily, Cicero (1994) proposed that alcohol-induced paternal effects may arise from damage to the genetic material in sperm, selection of certain populations of sperm based on as yet undefined criteria, and altered chemical composition of semen that may influence semen activity. Clearly, many unanswered questions remain about the role paternal alcoholism may play in causing birth defects in offspring—questions that can be explored through future animal studies.

Fetal Undernutrition

Perhaps one of the most important findings from animal models is that nutritional factors can contribute to alcohol's teratogenic effects (Dreosti 1993; Fisher 1988). Fetal undernutrition may result from maternal alcohol abuse in at least two ways. First, placental capacity to transfer nutrients to the fetus may be compromised by maternal alcohol abuse, even if the mother is adequately nourished. Second, a mother's drinking may make her undernourished, and thus, she may have suboptimal levels of essential nutrients to transfer to a fetus.

Normal growth and development during gestation requires the transfer of a constant supply of amino acids and glucose across the placenta from the mother to the fetus. Alcohol, however, directly inhibits the transport of amino acids (required for protein synthesis) and glucose (the cells' primary fuel source, which provides energy for protein synthesis and DNA replication) in placental tissue (Schenker et al. 1989; Snyder et al. 1986). Alcohol also significantly reduces glucose uptake in fetal neurons (Singh et al. 1992) and markedly retards growth, glucose metabolism, and protein synthesis in cultured rat embryos exposed to alcohol (Synder et al. 1992). Vitamin transfer also is impaired by maternal drinking: Placental transfer of a form of vitamin B_6 (involved in protein metabolism) from an alcoholic mother to her offspring decreases with alcohol exposure (Schenker et al. 1992). Alcohol-exposed offspring may continue to suffer from poor nutrition because of compromised gastrointestinal function caused by maternal alcohol ingestion (Guo et al. 1994). Thus, by depriving fetal tissues of essential energy sources and materials, alcohol exposure through maternal drinking impairs cell proliferation, growth, and differentiation in the fetus (Michaelis and Michaelis 1994).

Mechanisms of Alcohol Teratogenesis

Studies in experimental animals and in vitro models have helped to determine the molecular and cellular events affected by in utero alcohol exposure. Such studies have proposed numerous mechanisms that may underlie alcohol teratogenesis; the mechanisms currently held as most plausible have been addressed in various reviews (Michaelis and Michaelis 1994; Schenker et al. 1990).

For example, the teratogenic actions of alcohol may be mediated by direct actions on so-called ethanol-responsive genes, including tyrosine hydroxylase (Gayer et al. 1991) and modulators of G protein-coupled signal transduction in neuronal cells (Davis-Cox et al. 1996; Miles et al. 1993). Gene regulation by alcohol can explain alterations in protein synthesis and calcium regulation. Calcium (Ca^{++}) plays an important role in many signal transduction processes, and dysregulation of Ca^{++}-dependent processes at all developmental stages may influence cellular mechanisms of alcohol teratogenesis. Greater knowledge of the mechanisms of alcohol teratogenesis can have important implications for identifying a proximate teratogen that could aid risk assessment and lead to improved prevention strategies in humans.

Alcohol Versus Alcohol Metabolites

As alcohol is metabolized by the body, it is first converted to acetaldehyde by the enzyme alcohol dehydrogenase (ADH). Acetaldehyde, the primary metabolite of alcohol, is highly toxic; whether it is involved in alcohol teratogenesis, however, is unresolved. There is evidence that acetaldehyde reaches the fetus in rodents (Zorzano and Herrera 1989), sheep (Clarke et al. 1989), and humans (Karl et al. 1988), although in concentrations lower than observed in the maternal circulation. In addition, acetaldehyde alone can indeed induce malformations in midgestation embryo cultures of whole rat (Giavini et al. 1992).

Alcohol, however, is likely the key proximate teratogen for two reasons. First, acetaldehyde levels are usually very low in human alcoholics unless there is a genetic defect in the enzyme that metabolizes acetaldehyde to acetic acid (Eriksson and Fukunaga 1993). Second, experimental inhibition of ADH in pregnant mice, which decreases acetaldehyde levels and increases peak BACs, has increased the number of resorptions and the rate of skeletal malformations in the animal fetuses (see Michaelis and Michaelis 1994; Ukita et al. 1993).

Trophic Factors

The regulation and timing of growth processes in embryonic development are controlled by several tissue-specific trophic (pertaining to nutrition) or growth factors, including retinoic acid and nerve growth factor (NGF). Recent studies have provided significant findings concerning these various factors, which regulate cellular processes during maturation, proliferation, and differentiation.

Retinoic Acid

The birth defects that result from prenatal alcohol exposure are evidence that alcohol interferes with fetal development. Alcohol may directly disrupt developmental processes, or it may indirectly perturb development by competing for enzymes involved in the metabolism of other biologically important alcohols. Given alcohol's injurious effect on limb and CNS development, researchers have begun to explore whether alcohol may interfere with retinoic acid, a morphogen that regulates embryonic genes involved in limb formation and CNS patterning.

The enzyme ADH is thought to participate in the conversion of retinol, or vitamin A—a potentially potent teratogen—to retinoic acid, a strong morphogen and a regulator of the ADH_3 allele (Yang et al. 1994). Several researchers have hypothesized independently that alcohol administered prenatally acts by essentially usurping ADH activity and thereby limiting the conversion of retinol to retinoic acid. As a result, increasing levels of retinol accumulate in tissue, and the bioavailability of retinoic acid is reduced at times in development when it is needed to specify spatial patterns (Duester 1991; Grummer et al. 1993; Pullarkat, 1991). Grummer et al. (1993) demonstrated that alcohol reduced maternal serum levels of retinoic acid in rats. Alcohol-induced inhibition of neurite outgrowth (formation of axons and dendrites) in cultured human neuroblastoma cells was reversed with the addition of retinoic acid (Saunders et al. 1995).

The relationship among dietary vitamin A, circulating retinoic acid levels, and ADH activity is complex. The multiple forms of the human enzyme ADH, for example, vary in ability to metabolize retinol and are tissue specific in expression (Yang et al. 1994). Thus, the role of retinoic acid in mediating the effects of fetal alcohol exposure in humans remains to be determined.

Nerve Growth Factor

Alcohol also can interfere with the function of NGF, a neurotrophic factor that maintains neuronal survival, stimulates neurite outgrowth and cell growth, and induces enzymes involved in neurotransmitter synthesis. Heaton et al. (1992) noted that neurotrophic activity in extracts of fetal chick forebrain collected after alcohol exposure was significantly reduced, in terms of both influences on neuronal survival and neurite outgrowth. Dorsal root ganglia cultures from alcohol-exposed chicks were less sensitive to exogenous NGF (Heaton et al. 1992). Such impairments could result in reduced cell numbers and aberrant nerve cell connections, leading to various CNS deficits.

NGF, added to the system under certain conditions, may provide a neuroprotective effect against alcohol toxicity. Heaton et al. (1993) observed that inhibition of neurite outgrowth in dorsal root ganglia by lower doses of alcohol could be reversed by NGF (Heaton et al. 1993). NGF reversed a decrease in GABA neuron maturation in chick embryos (Brodie and Vernadakis 1992) and prevented or reversed the toxic effects of early exposure to alcohol on cholinergic neurons (Brodie et al. 1991).

Early exposure to stress hormones secondary to alcohol exposure may explain some of the exaggerated postnatal biobehavioral responses to stress after in utero alcohol.

Pantazis et al. (1992) showed that NGF limited the loss of cultured neuron-like rat tumor cells (PC-12) which accompanied high concentrations of alcohol. Because NGF arrests proliferation and induces differentiation, these results suggest that proliferating cells may be more susceptible to alcohol. However, differentiation (i.e., neurite outgrowth) in cultured human neuroblastoma cells without added NGF was inhibited by concentrations of alcohol that did not affect cell survival (Saunders et al. 1995). Astrocytes cultured from neocortex of mature rat fetuses exposed to alcohol throughout gestation showed increased concentrations of both cell surface and intracellular NGF receptors and an apparent increase in intracellular content of NGF, perhaps caused by decreased NGF secretion (Vallés et al. 1994). Such changes contribute to altered neuronal differentiation, migration, or both.

Glucocorticoids

Alcohol can activate the maternal HPA axis, causing elevated increases in corticosteroids in the mother and, through placental transfer, in the fetus (Weinberg and Bezio 1987). Because perinatal treatment with corticosteroids has been shown to produce runting (Taylor et al. 1988), several researchers have explored whether adrenocortical activation in a drinking mother may influence some of the effects of alcohol on a developing fetus and may be a potential mechanism for the interactive effects of prenatal stress and alcohol (Redei et al. 1993; Tritt et al. 1993). Pursuing this issue, Tritt et al. (1993) examined how the removal of adrenal glands in alcohol-exposed pregnant rats might affect birth weight of rat pups. The researchers found that removing the adrenal glands of pregnant rat dams before the animals began alcohol diets eliminated an alcohol-induced reduction in mean litter birth weight without altering alcohol-induced decreases in maternal weight gain (Tritt et al. 1993). The results suggest that an alcohol-initiated fourfold to eightfold increase in circulating maternal corticosteroid levels contributed to reduced fetal growth. In addition to a stress component in the etiology of FAS, these results imply that early exposure to stress hormones secondary to alcohol exposure may explain some of the exaggerated postnatal biobehavioral responses to stress after in utero alcohol (see McGivern and Riley 1993, Redei et al. 1993, Rudeen and Weinberg 1993, and Weinberg 1992).

Free Radical Damage

Anomalies associated with FAS may arise from excess oxygen-derived free radicals, such as superoxide anion (O_2^-), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2). These molecules, which are toxic byproducts of oxygen metabolism, contain unpaired electrons and are usually quite reactive, thus providing the potential for significant damage to biological tissue (Bondy 1992; Michaelis and Michaelis 1994). Damage to cells occurs because free radical molecules disrupt cellular integrity, targeting lipids, proteins, receptors, and chromosomes.

Cell membranes and membrane lipids appear to be particularly susceptible to alcohol-induced free radical damage during development (Arienti et al. 1993; Burmistrov et al. 1991; Devi et al. 1993; Murdoch and Edwards 1992). For example, alcohol administration increases the fluidity (a manifestation of membrane disorder or decomposition) of fetal hepatic mitochondrial membranes (Sanchez-Amate et al. 1992), brain membranes (Vorhees et al. 1988), and rat brain microsomes. This effect may result from alcohol metabolism or membrane adaptation to alcohol, rather than from direct actions of alcohol (Arienti et al. 1993).

Of the various disruptive effects of free radicals, lipid peroxidation has received considerable research attention. Lipid peroxidation is a process that readily modifies polyunsaturated lipids in the cell membrane, which can have powerfully adverse effects on the normal functioning of a cell. Fetal exposure to alcohol has been shown to increase levels of lipid peroxidation in various brain areas in rats, including the neocortex, hippocampus, and cerebellum (Petkov et al. 1992).

Free radical damage may explain regional differences in sensitivity to fetal alcohol because some tissues, such as neural crest cells, express lower levels of antioxidants (e.g, superoxide dismutase) than other tissues (Davis et al. 1990). Malformations associated with FAS, such as facial and cardiovascular defects, may arise from the damaging effects of free radicals because craniofacial and visceral structures derive from neural crest cells (Davis et al. 1990). In addition, fetal cells, on the whole, may be more sensitive to the damaging effects of free radicals because these cells have lower levels of antioxidants.

Studies exploring the effects of alcohol exposure also have shown that alcohol reduces the availability or activity of defense systems that normally protect cells from free radicals (Harris 1990), including decreased glutathione levels in rat brain and liver, and reduced alphatocopherol levels (vitamin E) in rat fetal hepatocytes (Devi et al. 1993; Reyes et al. 1993*b*; Tanaka et al. 1988; Weaver et al. 1993). The availability of antioxidants to combat alcohol-generated free radicals depends critically on diet, as well as smoking and other drug use, so that the proposed free radical mechanism of FAS is consistent with known risk factors for FAS (Abel and Hannigan 1995; Devi et al. 1993).

One implication of the relationship between lipid content of diets and susceptibility to alcohol-induced cellular damage (see Salem and Ward 1993) is that dietary supplementation with lipids that are critical to membranes or with antioxidants may mitigate the effects of alcohol on the fetus. For example, dietary supplementation with gangliosides (which are glycolipids)—specifically GM$_1$ (Hungund et al. 1993, 1994), omega-3 fatty acids (Wainwright et al. 1990*a,b*), vitamin E (Tanaka et al. 1988), or micronutrients such as zinc (which are cofactors for free radical scavenging enzymes) (Tanaka et al. 1983)—can decrease the impact of alcohol on fetal development (see below).

Hypoxia

Hypoxia, or lack of oxygen, has been called the most common cause of all cell death. In the fetus, hypoxia may play an important role in alcohol teratogenesis (Abel and Hannigan 1995; Michaelis and Michaelis 1994). Several lines of research provide support for this hypothesis. For example, alcohol constricts blood vessels of the placenta and umbilical cord in humans and in animals (Mukherjee and Hodgen 1982; Savoy-Moore et al. 1989), which produces profound effects on blood flow (Taylor et al. 1994*a*). Alcohol also has been shown to induce a significant rise in blood pressure in perfused, isolated human placental lobules; this effect can be reversed by indomethacin (an agent that suppresses prostaglandin production) (Taylor et al. 1994*a*). Maternal drinking can suppress fetal "breathing" movements, a sensitive index of fetal hypoxia, in humans and animals (McLeod et al. 1983). Finally, prenatal hypoxia can produce effects that are similar to alcohol's effects (Janicke and Coper 1994); such effects can persist well into childhood (Korkman et al. 1994).

Arishima et al. (1993) showed that acute maternal alcohol intake caused a constriction of the rat ductus arteriosus (a vessel that conducts blood between placenta and fetal heart). The investigators suggest that alcohol may produce this effect through a glucocorticoid-induced reduction in prostaglandins, metabolites of fatty acids that control vascular rigidity (Arishima et al. 1993). If placental-fetal blood flow is predictive of the effects in humans of fetal alcohol exposure, then recent advances in sophisticated Doppler velocimetry and ultrasonography may enable detection of subtle blood-flow changes and identification of fetuses at risk for FAS (Kochenou 1993; Yoon et al. 1993).

Hypoxia induces a cascade of cellular events (e.g., decreased NA$^+$-K$^+$-ATPase activity and protein synthesis and increased lactate production) that also have been documented after prenatal alcohol exposure (see Abel and Hannigan 1995 and Michaelis and Michaelis 1994). Certain brain areas (e.g., the hippocampus) may be more vulnerable to alcohol-induced hypoxia because they are richly vascularized and more densely populated with neurons that release glutamate, an excitatory amino acid neurotransmitter (Diemer et al. 1993). Excess release of these neurotransmitters during hypoxia or fetal alcohol exposure or both can cause excitotoxic cell damage (Michaelis 1990).

Finally, hypoxia can increase the levels of free radicals (Michaelis and Michaelis 1994), which can damage the cell surface and allow calcium to leak into and accumulate in cells. Abnormal accumulation of calcium in nerve cells may cause them to release excess neurotransmitters that, in turn, can have toxic effects on certain cells.

Of note, however, are findings that suggest that hypoxia may not be involved in alcohol teratogenesis. Smith et al. (1989) exposed near-term pregnant sheep to doses of alcohol equivalent to binge-type drinking. The investigators found that such exposure did not produce fetal hypoxia or acidosis. Thus, the body of literature in this research area indicates that hypoxia is an interesting potential mechanism, but more research clearly is needed.

Summary

Maternal drinking can produce a spectrum of harmful effects in exposed offspring, ranging from a characteristic pattern of gross morphological anomalies and mental impairment to more subtle cognitive and behavioral dysfunctions. FAS is the most severe clinical outcome of prenatal alcohol exposure; three clinical criteria are used to diagnose the syndrome. ARBD and FAE are used to describe individuals who exhibit only some of the attributes of FAS and do not fulfill the diagnostic criteria for FAS.

For various reasons, clinicians and researchers continue to have difficulty identifying individuals with FAS. For example, none of the characteristic abnormalities of the syndrome is specific to the diagnosis. In addition, specific facial abnormalities can be subtle and difficult to recognize, their expression can change as a person ages, and their severity may vary among individuals and among different racial and ethnic groups. The challenge may be even greater in identifying children and adults who exhibit only some of the attributes of FAS. Although these individuals may not fulfill the diagnostic criteria for FAS, they can have behavioral and cognitive problems that persist with age and can restrict normal functioning.

Researchers are examining various tools that can improve and simplify efforts to diagnose FAS. Among these tools are computer-assisted techniques that facilitate morphometric analysis of facial features of people with FAS, behavioral profiles of people who are affected by prenatal alcohol exposure, and imaging techniques that can reveal markers of alcohol-induced injury in the brains of affected individuals.

Studies are beginning to reveal how people with FAS develop as they age. Recent findings indicate that the deficits associated with FAS are pervasive and long lasting. Although many of the physical characteristics become less prominent after puberty, intellectual problems endure and behavioral, emotional, and social problems become more pronounced. One study reported that arithmetic skills in adolescents and adults with FAS were at the second- to fourth-grade levels; these individuals have particular problems with abstractions, such as cause and effect or time and space, as well as generalizing from one situation to another. Such deficits had a marked effect on an individual's ability to live independently.

Children with FAS and ARBD frequently are described as being hyperactive and impulsive and having short attention spans. Maladaptive behaviors, such as poor judgment, failure to consider the consequences of one's actions, and difficulty perceiving social cues, can be common, even among alcohol-affected persons who are not considered to be retarded according to IQ scores.

Prospective longitudinal studies are providing knowledge about the full spectrum of deficits that may result from in utero exposure to alcohol. These studies consider the scope of drinking practices among women and thus provide an opportunity to measure the relationship of quantity, frequency, timing, and pattern of drinking to infant and child outcome. Findings from some, but not all, prospective studies have revealed an association between prenatal alcohol exposure and growth deficits at birth; these deficits have been found to persist in infants 6 to 8 months after birth and in children 6 years of age. Prospective studies also have reported a range of behavioral and cognitive deficits in infants exposed to alcohol in utero.

Studies have yet to reveal fully how the timing of alcohol exposure, dose response, and maternal drinking patterns disrupt particular stages of fetal development. According to several longitudinal studies, first-trimester exposure to alcohol is associated with craniofacial anomalies in children. The association between timing and growth, however, is not as clear, perhaps due to the varying postnatal stressors and doses of alcohol exposure in the different studies. Alcohol-induced neurobehavioral effects also may be sensitive to periods of exposure during development. For example, heavy maternal alcohol use during the first and second trimesters appears to increase the occurrence of delayed language development in children.

Because alcohol-induced birth defects are completely preventable with maternal abstinence from alcohol, prevention is a central research issue. It is unlikely that one prevention approach can be devised to target effectively all alcohol-abusing pregnant women, because high-risk drinking is influenced by multiple factors. Researchers are working toward developing multilevel strategies that, optimally, can interact to enhance prevention outcome. Within the multilevel approach are community education programs to increase general awareness of the hazards of drinking during pregnancy, approaches to effectively identify women whose drinking places them at risk for adverse pregnancy outcomes, and strategies aimed at intervening with individual women who are problem drinkers and thus at greatest risk for having a child who is affected by alcohol.

Animal studies are an extremely productive area of FAS research. Animal models and in vitro biological systems present some significant advantages for studying alcohol-induced damage in a developing fetus. Such models enable researchers to conduct controlled experiments to examine how the complex pharmacologic, biochemical, and physiologic effects of alcohol are affected by and interact with the various genetic, experiential, social, and behavioral factors that influence alcohol's effects in humans. Unlike in clinical studies, this analysis can sometimes be performed in hundreds of animals, thereby greatly increasing the power of observations. Animal models also enable researchers to control, exclude, and measure potent factors that may confound understanding of FAS and ARBD in studies of human populations.

Researchers have used animal models to explore a critical question: How much alcohol is too much? Controlled animal experiments have demonstrated that peak maternal BAC determines the likelihood and magnitude of alcohol-induced impairments. Thus, the total amount of absolute alcohol consumed and the pattern of alcohol drinking (such as rapid drinking over a short period) are both critical factors influencing fetal outcome. In addition, animal studies have demonstrated that the period(s) during pregnancy when BACs are high has important influence on the variable expression of ARBD.

The consequences of alcohol exposure are similar in animals and in humans. In general, animal studies demonstrate that prenatal alcohol exposure causes poor somatic growth, malformation of major organs, craniofacial anomalies, and associated CNS dysfunction.

Animals exposed prenatally to alcohol also exhibit neurobehavioral problems such as hyperactivity, perseveration, poor balance and coordination, difficulty walking, and inability to learn from past experiences. Rodent models have helped to elaborate the nature of age-dependent behavioral hyperactivity and learning deficits. For example, maternal alcohol consumption in rats disrupts spatial and temporal-pattern learning in offspring.

Determining how prenatal exposure injures the developing brain is a critical concern because of the persistent and often severe neurobehavioral and cognitive impairments of FAS and ARBD. Prenatal alcohol exposure can produce profound anatomical changes in the fetal CNS by altering cell proliferation, migration, differentiation, and pruning. Dose, duration, and pattern and timing of exposure can influence the specific neuroanatomical outcomes. For example, prenatal alcohol exposure during differentiation of cerebellar Purkinje cells causes significant loss of these cells, whereas exposure to equivalent doses during cell formation does not affect cell numbers. Alcohol also appears to have concentration and time-dependent effects on neural tube formation.

Prenatal exposure may also affect proper development and function of glial cells, which are nonneural cells in the brain. Alcohol disrupts myelination and the maturation of astrocytes and glial cells; such perturbations may contribute to brain defects associated with prenatal alcohol exposure. For example, alcohol's effects on glial cells could disrupt migration of neurons guided by these cells, producing the misplacement of neurons that occurs with FAS.

Finally, animal studies indicate that prenatal alcohol exposure affects neurotransmitter systems in the brain, including the serotonin, dopamine, acetylcholine, glutamate, and GABA systems. The nature of the neurotransmitter dysfunction may depend critically on when alcohol exposure occurs in development.

Studies using experimental animals and in vitro models have helped to determine the molecular and cellular events affected by in utero alcohol exposure. Such studies have helped to elaborate the role of acetaldehyde, trophic factors (retinoic acid, nerve growth factor, and glucocorticoids), free radical damage and membrane lipids, and hypoxia in alcohol-induced fetal damage. Greater knowledge of the mechanisms of alcohol teratogenesis can have important implications for identifying a proximate teratogen that could aid risk assessment and lead to improved prevention strategies in humans.

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Chapter 7

Effects of Alcohol on Behavior and Safety

Introduction

Extensive research has shown that alcohol use and abuse directly and indirectly affect many human behaviors with potentially serious consequences for the well-being of society. More than 100,000 deaths each year in the United States result from alcohol-related causes (National Safety Council 1994). Motor vehicle crashes, falls, fires, and drownings cause more than 75 percent of all deaths from unintentional injuries (Baker et al. 1992), and alcohol use has been associated with a large percentage of these deaths. Alcohol use has been implicated in 15 to 63 percent of fall fatalities, in 13 to 37 percent of nonfatal injuries from falls, and in 33 to 61 percent of burn fatalities (Hingson and Howland 1993). Drinking has been associated with high-risk sexual behavior (Strunin and Hingson 1992, 1993), family and marital violence, homicide, physical assault, and involvement in other criminal activities (Martin 1992). These adverse consequences of drinking affect persons of all ages and backgrounds.

The causal mechanisms through which alcohol use contributes to intentional and unintentional injury are not fully understood. However, some researchers have proposed that alcohol and injury interact through behavioral-contextual and biological mechanisms (Li et al. 1994). For behavioral-contextual interactions, the context and the place in which an individual consumes alcohol may increase the risk of injury. For example, drinking in bars where the risk of assault may be high likely exposes an individual to more hazardous circumstances than drinking at home. Increased risk of injury also may be caused by direct biological effects of alcohol—those that impair an individual's ability to perceive and respond to hazards. These effects clearly are at work in a large proportion of motor vehicle-related injuries in this country (Council on Scientific Affairs 1986). Biological effects of alcohol may be further divided into effects of increased injury risk as blood alcohol levels rise, and hangover or other longer term effects that may increase injury risk even when blood alcohol is undetectable (Li et al. 1994).

This chapter considers the relationship between alcohol use and intentional or unintentional injury and death. The chapter begins with a review of findings from studies of emergency room (ER) patients and data from death certificates. Results of research on the role of alcohol use in traffic crashes, burns and fires, drownings and boating accidents, airplane crashes, and occupational injuries also are presented. Studies describing the relationship of alcohol use to interpersonal violence are then reviewed, followed by an overview of the impact of risk-taking behavior related to alcohol use, such as drinking and driving and high-risk sexual behavior.

Trauma

Trauma is a significant problem in many countries. According to Kochanek and Hudson (1995), accidents and adverse effects were the fifth leading cause of death in the United States in 1992. Alcohol can impair motor coordination, balance, attention, perception, and judgment. These effects may play a major role in serious and fatal traumatic injuries (Baker et al. 1992; Cherpitel 1992), including those sustained in motor vehicle crashes (Cherpitel 1992); fires, falls, and drownings (Hingson and Howland 1993); occupational hazards (Webb et al. 1994); and interpersonal and family violence (Martin 1992).

Researchers use various measures and information sources to assess alcohol consumption and its relationship to injury or death. Among these are blood alcohol concentrations (BACs) (table 1), biochemical markers of alcohol consumption, self-reports or collateral reports of drinking behavior, and medical examinations and diagnoses of alcoholism and alcohol-related problems (Harford 1993). Data on alcohol-associated traumatic injuries come from several sources:

- ER reports
- Coroner or medical examiner reports
- Case-control studies, which compare past and current patterns of alcohol use of injured persons with those of matched noninjured control subjects
- Prospective studies, which follow cohorts of alcohol users or persons with alcoholism over time and record events as they occur (Cherpitel 1992)

Certain factors may hamper measurement of alcohol-related casualties, such as the absence of appropriate control or comparison groups in some studies, a lack of information about the drinking habits of persons who die as a result of injury, a bias toward underreporting alcohol-related conditions on death certificates, and the absence of systematic procedures for reporting and recording the involvement of alcohol in injuries (Harford 1993). However, in 1990, the International Conference for the 10th Revision of the *International Classification of Diseases* (ICD-10) and the World Health Assembly approved coding for alcohol involvement in casualties, an action that should improve systematic reporting practices.

Some evidence suggests that alcohol use may adversely affect the outcome of injury.

Despite methodological difficulties, the literature clearly shows that alcohol has a significant impact on the risk for accidental injury or death. For example, using data from the 1986 National Mortality Followback Survey (Seeman 1992), a recent study by Li et al. (1994) compared drinking patterns of 6,355 persons aged 25 to 64 years who died as a result of either injury or disease. The study showed that those who died of injury drank more frequently and more heavily than those who died of disease (Li et al. 1994). The same study found that daily drinking, binge drinking (defined as the consumption of 5 or more drinks per occasion), and heavier drinking (defined as consumption of 14 or more drinks per week) increased the likelihood of injury as the underlying cause of death. In another study, Rivara et al. (1993*a)* found that of 2,657 patients admitted to an ER for treatment of blunt or penetrating trauma, 47 percent had a positive BAC (0.01 percent or greater) and about 36 percent were intoxicated (BAC of 0.10 percent or greater) (table 2). Intoxicated patients were more likely to be in the 25- to 34-year-old age group and to be male and nonwhite, and the highest proportion of intoxicated patients was found among victims of stab wounds (Rivara 1993*a*).

Some evidence suggests that alcohol use may adversely affect the outcome of injury. For example, ER and coroner report studies show that alcohol use is more prevalent in fatal than in nonfatal injuries, suggesting an influence of alcohol on the severity of injury (Cherpitel 1992). However, this is an area of debate. Honkanen and Smith (1990) have observed both positive and negative associations (depending on the type of injury) between alcohol intoxication and injury severity. Jurkovich et al. (1993), however, found no association between acute intoxication and increased risk of complications or death due to injury in a prospective study of 3,564 patients admitted to a trauma center with injuries, although chronic alcohol use was associated with longer hospital stays and an increased risk for injury-related complications. Positive associations between alcohol use and injury severity may be observed, in part, because people who have severe injuries may reach the ER sooner and may be more likely to have positive BACs. Conversely, negative associations may be observed because intoxication may bias injury severity measures

Table 1. Physiologic significance of different levels of blood alcohol concentration (BAC).

BAC %*	Physiologic Significance
0	Negative BAC—normal level of blood alcohol
0.01	Positive BAC†
0.05	Legally impaired (in some countries)
0.10	Under the influence—legal level for intoxication (in most States in the U.S.)
0.15	Very intoxicated‡

*Percentages reflect the number of milligrams (mg) of alcohol found in 100 milliliters (mL) of blood; that is, a BAC of 0.01 percent is equal to 10 mg of alcohol in 100 mL of blood.
†0.01 percent is used to designate positive BAC in most studies.
‡Level of intoxication varies per person, depending on such individual characteristics as weight, metabolism, and food already in the stomach.
Source: 1982, 1987, 1990, and 1993 NDATUS Surveys.

Table 2. Characteristics of nonintoxicated and intoxicated trauma patients (N = 2,657).

		Percent	
Characteristic	**Number**	**Non-intoxicated (n = 1,705)**	**Intoxicated* (n = 952)**
Total	2,657	64.2	35.8
Age (years)			
18–24	692	68.5	31.5
25–34	817	56.8	43.2
35–44	550	60.2	39.8
45–54	261	62.5	37.5
55–64	139	72.9	28.1
≥ 65	198	87.4	12.6
Sex			
Male	2,040	60.1	39.9
Female	617	77.6	22.4
Race			
White	1,900	68.1	31.9
African American	413	53.8	46.2
Asian	129	77.5	22.5
Hispanic	116	51.7	48.3
Native American	97	28.9	71.1
Injury Mechanism			
Motor vehicle occupant	839	69.2	30.8
Motorcycle	220	68.2	31.8
Pedestrian	185	68.1	31.9
Fall	398	61.8	38.2
Stab	246	43.1	56.9
Gunshot	224	67.9	32.1
Blunt, not specified	385	57.1	42.9
Penetrating, cutting, not specified	82	76.8	23.2
Other	78	78.2	21.8
All blunt	2,105	65.8	34.2
All penetrating	552	58.0	42.0
Intent			
Unintentional	1,890	70.5	29.5
Assault	587	45.7	54.3
Self-inflicted	118	64.4	35.6
Other (including legal, unknown)	11	72.7	27.3
Disposition			
Discharged alive	2,434	63.6	36.4
Died in hospital	223	70.0	30.0

*Intoxication is defined as blood alcohol concentration at or above 0.10 percent.
Source: Rivara et al. 1993*a*. Reprinted by permission. *Archives of Surgery* 128:909,1993. Copyright 1993, American Medical Association.

upward (e.g., if symptoms of intoxication are interpreted as symptoms of a serious head injury), producing an apparently higher rate of survival among those with higher BACs (Waller 1988).

In addition, alcohol abuse may increase the risk for repeated injuries. Rivara et al. (1993*b*) recently conducted a prospective study examining the relationship between acute alcohol intoxication or chronic alcohol abuse and the risk of repeated admission to the ER for trauma in a large sample of patients. Intoxicated patients (those who had a BAC of at least 0.10 percent at initial admission) were 2.5 times more likely to be readmitted for trauma than patients who were not intoxicated. Certain sociodemographic factors, including male gender, minority ethnic status, and use of Medicaid, also were associated with an increased likelihood of readmission. The risk of readmission was highest for victims of assault. However, statistical adjustment to control for demographic characteristics and mechanism of injury revealed that acute or chronic alcohol abuse itself was an important risk factor for reinjury (Rivara 1993*b*).

Emergency Room and Coroner Report Studies

Many of the data supporting a relationship between alcohol use and accidental injury or death have come from ER and coroner report studies. Coroner reports are the main source of information on alcohol-associated fatalities and can be used to directly compare alcohol use across type of injury and various demographic characteristics. Data on alcohol-associated nonfatal injuries come largely from ER studies. ER studies also may consider type of injury and demographic characteristics and often include information on self-reported drinking behaviors before and after an injury event.

ER studies have yielded prevalence estimates of positive BACs (greater than 0.01 percent) across all types of nonfatal injuries that range from 6 to 34 percent of representative samples (Cherpitel 1993*a*). The wide range in prevalence estimates may be related in part to variation in the demographic characteristics of ER populations, such as ethnicity, gender, marital status, and age (Cherpitel 1992, 1993*a*). ER studies also have suggested that positive BAC values (0.01 percent or greater) are more prevalent among ER patients who are injured than among those seeking care for non-injury-related medical problems (Cherpitel 1994*b*). In studies of coroner reports, prevalence estimates of positive BAC range from 44 to 47 percent among persons who died from unintentional injuries (Abel and Zeidenberg 1985; Berkelman et al. 1985). As mentioned earlier, data from both ER and coroner report studies have shown that alcohol use is more prevalent in fatal than nonfatal injuries. One study that examined ER and coroner report data for a single county found that 32 percent of patients who had fatal injuries had BACs of 0.10 percent or greater, whereas only 6 percent of nonfatally injured patients had BACs in this range (Cherpitel 1994*a*). (For more discussion of coroner report studies, see the *Eighth Special Report to the U.S. Congress on Alcohol and Health.*)

Populations of ER patients may differ according to the health care systems they access, and such differences may influence the prevalence of alcohol-related ER admissions. To examine this influence, Cherpitel (1993*c*) compared BAC values and self-reported data from representative samples of patients from two distinctly different health care systems in a suburban area within the same county. One sample was drawn from the county hospital and three community hospitals; the second sample was drawn from three health maintenance organization (HMO) hospitals. Similar associations between alcohol consumption and injury status were observed for both samples: Injured patients were significantly more likely than noninjured patients to have a positive BAC and to report heavy drinking, more frequent drunkenness, and prior alcohol-related traffic crashes. Injured patients also were more likely to report a history of treatment for alcohol-related problems. However, patients in the county and community hospital sample reported higher rates of frequent heavy drinking, alcohol-related problems, and prior alcoholism treatment than those in the HMO sample. These differences may have been explained by sociodemographic differences between the public hospital population and the HMO population (Cherpitel 1993*c*).

Cultural differences also may influence the role of alcohol in injuries. A study by Cherpitel et al. (1993) considered the effect of drinking on injury status among patients aged 18 years and older given ER treatment in Contra Costa County, California; Mexico City, Mexico; and Barcelona, Spain. These researchers found that factors related to drinking in the injury event, such as drinking companions, place of alcohol-related injury, perceived drunkenness at the time of injury, and causal attribution of drinking to injury, varied among the three groups. For example, compared with men and women in the Contra Costa County or Barcelona samples, men and women in the Mexico City sample were more likely to report feeling drunk at the time of the injury but less likely to attribute the injury to consumption of alcohol. In the Barcelona sample, both men and women were less likely than those in the other groups to report feeling drunk at the time of injury, but were more likely to attribute the injury to alcohol use. Cherpitel et al. (1993) concluded that for different cultures, the context in which alcohol-related injuries occur is affected by the context in which alcohol is typically consumed, and is important for understanding the role of alcohol in injury and in situations that may be high risk for alcohol-associated injury. In addition, these findings illustrate that studies comparing data from different countries or different ethnic or racial populations should appreciate and account for cultural differences in definitions of qualitative concepts such as drunkenness or causal attribution (Cherpitel et al. 1993).

> *Motor vehicle crashes are the leading cause of death among persons aged 1 to 34 years in the United States.*

Traffic Crashes

Motor vehicle crashes are the leading cause of death among persons aged 1 to 34 years in the United States (National Center for Health Statistics 1994). In 1993, a total of 40,115 people lost their lives in traffic crashes; another 3.1 million people were injured (National Highway Traffic Safety Administration [NHTSA] 1994*a*). Persons aged 16 to 20 years had the highest injury and fatality rates per 100,000 population (NHTSA 1994*a*).

The extent of loss, pain, and injuries sustained from alcohol-related traffic crashes is great. NHTSA (1994*b*) has estimated that 7 percent of all crashes and 44 percent of fatal crashes in 1993 involved alcohol use. That year, nearly 17,500 people died and 289,000 people were injured in alcohol-related traffic crashes. In addition, 35 percent of all traffic fatalities (13,984 deaths) resulted from crashes in which at least one driver or nonoccupant was legally intoxicated (BAC of 0.10 percent or greater). More than two-thirds of the people killed in such crashes, including drivers, pedestrians, and bicyclists, were intoxicated; approximately one-third were passengers, nonintoxicated drivers, or nonintoxicated nonoccupants (NHTSA 1994*b*) (table 3). In terms of years of potential life lost[1] (YPLL), a measure of the human cost of premature death due to a particular cause, alcohol-related traffic fatalities resulted in 353,734 YPLL for men and 106,676 YPLL for women in 1993. These figures represent 44 and 32 percent, respectively, of the total YPLL for all traffic crashes in 1993 (Campbell et al. 1995) (see Chapter 1, Epidemiology of Alcohol Use and Alcohol-Related Consequences, for a discussion of the epidemiology of alcohol-related traffic crashes).

In recent years, however, there has been an encouraging reduction in the number of alcohol-related traffic fatalities. The proportion of deaths from such crashes declined steadily over the years from 1983 to 1993 (NHTSA 1994*b*). The 44-percent figure for fatal alcohol-related crashes in 1993, given above, represents a drop of 2 percent from 1992 and a reduction of 26 percent from 1983 (NHTSA 1994*b*). Similarly, the number of intoxicated drivers killed in traffic crashes decreased by 28 percent between 1983 and 1993. The greatest reductions were observed among the oldest and youngest drivers—44 percent for those over 65 years old and 47 percent for those between 16 and 20 years old (NHTSA 1994*b*).

Among young drivers (aged 16 to 24), the number killed in alcohol-related traffic crashes decreased by 40 percent between 1977 and 1993 (Campbell et al. 1995). Legislation that raised the minimum drinking age from 18 to 21 years has contributed to the decline in alcohol-related highway crashes reported for teens (O'Malley and Wagenaar 1991). This study found that higher minimum drinking age was associated with lower levels of alcohol use among high school seniors and recent high school graduates. The authors suggested that an important factor in the lowered rate of crashes for people under age 21 is the decreased amount of time they spend in bars when the minimum drinking age is 21 rather than 18 (O'Malley and Wagenaar 1991) (see Chapter 8, Economic Aspects of Alcohol Use and Alcohol-Related Problems, for a discussion of alcohol use by minors).

Table 3. Types of fatalities in fatal crashes involving at least one intoxicated driver or nonoccupant, 1993.

Type of Fatality	Number	Percentage of Total
Intoxicated Drivers	7,578	54
Nonintoxicated Drivers	938	7
Passengers	2,917	21
Intoxicated Nonoccupants (pedestrians and pedalcyclists)	1,936	14
Nonintoxicated Nonoccupants	615	4
Total Fatalities	13,984	100

Source: National Highway Traffic Safety Administration 1994*b*.

Between 1977 and 1993, the number of male drivers of all ages involved in fatal alcohol-related crashes declined by 22 percent. In contrast, the number of female drivers involved in such crashes increased by 18 percent. Despite this increase, in 1993, the total number of fatal traffic crashes involving women drivers with BACs of 0.10 percent or greater (1,581) remained far below that of men (9,365) (NHTSA 1994*b*).

Alcohol-related fatal and nonfatal traffic crashes tend to occur at times that parallel peak periods of alcohol consumption, such as night time and weekends. NHTSA (1994*b*) reported that alcohol involvement in fatal crashes was more than three times higher at night than during the day (65.3 versus 19.5 percent); for all alcohol-related crashes, alcohol involvement was about six times higher at night than during the day (14.7 versus 2.5 percent). Analysis of 1993 data revealed that alcohol had been consumed in 4 percent of all crashes and in 33.5 percent of all fatal crashes that occurred on weekdays, whereas on weekends, alcohol had been consumed in 12 percent of all crashes and 56.9 percent of all fatal crashes (NHTSA 1994*b*).

The type of motor vehicle driven appears to be relevant to the occurrence of alcohol-related traffic crashes (NHTSA 1994*b*). Among drivers of various types of vehicles involved in fatal crashes in 1993, motorcycle operators had the highest intoxication rates (BAC of at least 0.10 percent) in 1993: 32.9 percent of all motorcycle drivers involved in fatal traffic crashes were intoxicated compared with 24.9 percent of drivers of light trucks, 20.7 of passenger car drivers, and 1.7 percent of drivers of large trucks (NHTSA 1994*b*).

In summary, alcohol-related crashes contribute significantly to injury and loss of life in the United States. These crashes tend to occur at peak periods of alcohol consumption, such as night time and weekends, and are more frequent among motorcycle drivers than among drivers of other types of vehicles. The numbers of alcohol-related crashes have declined in recent years, particularly among younger and older drivers, but have increased among women.

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[1] Years of potential life lost is calculated by subtracting the age of death for each individual death from expected life expectancy in a population and summing the total across all deaths in that population.

Impairment of Driving Ability

Alcohol can affect driving ability by interfering with psychomotor skills (those involving brain-hand coordination) and cognitive skills, such as information processing. The effects of drinking on driving ability is dose related, and a driver's risk of being in a fatal crash nearly doubles with each percent increase in BAC (Zador 1991). BACs as low as 0.02 percent can impair drivers' ability to divide their attention between two or more tasks—a critical effect in that safe driving requires the performance of multiple tasks concurrently (Moskowitz and Burns 1990). Low to moderate BACs (0.03 to 0.05 percent) interfere with voluntary eye movements and impair the driver's ability to rapidly track a moving target (Baloh et al. 1979; Busloff 1993; Katoh 1988). At BACs of 0.05 percent and higher, performance decreases significantly on measures of reaction time, information processing, vigilance, and psychomotor skills (Moskowitz and Robinson 1987). One study has shown that persons who drank moderate amounts of alcohol (to yield BACs of approximately 0.05 to 0.06 percent) reported feeling inebriated and recognized that certain abilities, such as walking in a straight line, were compromised by alcohol intake but failed to report any change in their ability to drive (Hindmarch et al. 1992).

BACs as low as 0.02 percent can impair drivers' ability to divide their attention between two or more tasks—a critical effect in that safe driving requires the performance of multiple tasks concurrently.

The degree to which alcohol induces impairment may vary with age. Laboratory data suggest that increasing age may magnify the adverse effects of low doses of alcohol on tracking (Linnoila et al. 1980). For younger drivers, alcohol use may be especially risky because they have comparatively little experience with alcohol (i.e., tolerance) or with driving (Zador 1991; Zobeck et al. 1993).

Some studies suggest that alcohol's impact on perceptual and motor skills related to driving ability also may vary with gender. Jones and Jones (1976) have demonstrated that women show greater cognitive and psychomotor impairment than men after consuming the same dose of alcohol. However, when alcohol doses have been adjusted so that men and women attain similar BACs, gender-related differences generally have not been observed (Niaura et al. 1987). Hindmarch et al. (1992) have shown that when alcohol was given in doses yielding equivalent, moderate to intoxicating BACs in men and women, no clear differences were observed on tests of cognitive skills related to driving ability. However, men performed more poorly than women on tasks assessing general central nervous system activity and short-term memory, and women performed more poorly on a motor performance test assessing reaction time. These differences were observed even after controlling gender-related differences in performance before alcohol consumption.

Characteristics of Drinking Drivers

Several studies have examined whether drinking drivers demonstrate identifiable characteristics that may influence alcohol use and traffic safety. Gender, age, and particular personality features appear to be associated with the risk of drinking and driving. For example, intoxicated drivers involved in fatal crashes are more likely to be males than females. Moreover, those who drive under the influence of alcohol are more likely to be between the ages of 16 to 34 years than 35 years or older (NHTSA 1994*b*). Although only 15 percent of licensed drivers in 1993 were between 16 and 24 years of age, persons in this age group accounted for more than 28 percent of drinking driver deaths (Campbell et al. 1995). Finally, studies have revealed that, as a group, persons convicted of driving while under the influence of alcohol (DUI) may be characterized as having higher levels of hostility, sensation seeking, irritability, driving aggression, and competitive speed compared with the general driving population (Donovan et al. 1985; Jessor 1987). These and other characteristics of the DUI population may have important implications for the development of targeted prevention and treatment strategies.

Additional studies suggest that there may be differences in characteristics among DUI offenders; such differences may influence treatment effectiveness. In a study of young drinking drivers (aged 18 to 23) grouped according to whether they were stopped at a roadblock or apprehended in a traffic crash or moving violation, McMillen et al. (1991) noted that alcohol use within both groups was significantly greater than within the nondrinking driver population. However, DUI offenders apprehended in traffic crashes or moving violations were more hostile and had more drinking-related crashes and nontraffic arrests and more drinking and driving occasions compared with drinking drivers apprehended at roadblocks. Those apprehended at roadblocks differed from nondrinking drivers only on measures of sensation seeking and frequency of drinking and driving.

In an extension of this study, McMillen et al. (1992*b*) examined six groups of drivers—four groups of drinking drivers and two groups of nondrinking drivers—to further identify traits, behaviors, and attitudes of drinking driver subtypes. Results indicated that persons apprehended for DUI in traffic crashes or moving violations were the highest risk group. They differed significantly from the remaining groups as a whole on measures of personality, behavior, and attitude. The investigators suggested that being apprehended for DUI under these conditions may signify more general problem behaviors; thus, these individuals may require different interventions from those used for other DUI offenders.

Evidence also indicates that multiple and first-time DUI offenders have dissimilar characteristics. Having multiple DUI convictions suggests that a person is unable to avoid behaviors that potentially lead to adverse consequences. To examine this issue, McMillen et al. (1992*a*) compared first-time and multiple DUI offenders and noted that the two groups differed significantly on measures of personality traits, drinking behaviors and problems, and driving behavior and history. For example, multiple offenders had more traffic crashes and traffic violations than first-time offenders and also were more likely to have been arrested for a misdemeanor or felony charge. In addition, alcohol intake and problems were greater among multiple offenders than among first-time offenders. Various personality traits, including assertiveness and emotional adjustment ability, also differentiated the two groups. Overall, multiple offenders demonstrated personality traits and behaviors suggesting that these individuals may differ from alcohol abusers in general and that the behavior of multiple offenders may be characteristic of a general lifestyle of problem behaviors (Jessor 1987).

Drivers convicted of DUI tend to consume alcohol frequently and in large amounts (Gruenewald et al. 1990), have high BAC values (Perrine et al. 1988), and score high on instruments used to screen for alcoholism (Snowden et al. 1986). A study of male drivers and motorcycle riders injured in alcohol-related crashes shows that as BAC values increased, so did the frequency of drinking and driving and the likelihood of a previous license suspension due to drinking and driving (Holubowycz and McLean 1995). In addition, approximately one-fourth of men with BACs of at least 0.15 percent were probably experiencing alcohol-related problems before the crash occurred (based on responses to interview questions, scores on an assessment scale for alcohol dependence, and tests for elevated levels of a liver enzyme), whereas only a small percentage of those with lower BACs were experiencing such problems. Problem drinkers also are more likely than persons without drinking problems to be repeatedly charged with driving while intoxicated (DWI) and to underreport or underestimate the frequency of self-reported drinking and driving events (Yu and Williford 1993*b*).

In the United States, males are more likely to drink and drive. A study of convicted drunk drivers in Michigan found that men were disproportionately overrepresented and also showed a high recidivism rate for drunk driving among offenders: 47.2 percent of offenders had at least one prior conviction of driving while alcohol impaired or driving while intoxicated (Eby 1995). Because females constitute a small proportion of persons convicted of DUI, research on these women is limited (Shore et al. 1988; Yu et al. 1992). A recent study conducted in New York State has examined gender-based distribution of and recidivism to drinking and driving among persons convicted of driving while intoxicated/driving while ability impaired (DWI/DWAI) (Yu et al. 1992). This study revealed that from 1978 to 1988, the convicted population of drinking drivers was primarily male. During the study period, however, the proportion of females convicted of DWI/DWAI steadily increased. In addition, the rate of recidivism to DWI/DWAI increased more rapidly for females than for males (Yu et al. 1992). Changes in women's roles and lifestyles, changes in attitudes of the public and police toward female drinking drivers, and the impact of increasing the legal drinking age to 21 may have contributed to gender-associated changes in the population of DWI/DWAI offenders (Yu et al. 1992).

Burns and Fires

Burns and fires cause about 5,000 deaths and about 1.4 million injuries annually (Baker et al. 1992). Approximately one-half of the adults who die in house fires have high BAC values, a finding that is consistent with the disproportionate number of deaths that occur in house fires on weekends, when people tend to consume more alcohol (Baker et al. 1992).

Alcohol may contribute to burns and fires by causing drowsiness and increasing the likelihood of falling asleep while smoking. In addition, intoxication may reduce awareness of smoke and fire alarms and may interfere with escape from a burning building by increasing disorientation associated with smoke and panic.

A review of five recent U.S. studies shows that between 33 and 61 percent of persons who died as a result of burns were drinking (Hingson and Howland 1993). Two additional studies showed alcohol involvement in 22 and 26 percent, respectively, of persons with burn injuries (Cherpitel 1989; Jones et al. 1991).

Alcohol use also appears to have an impact on the outcome of burn injuries. A recent retrospective study has examined the role of alcohol in injury outcome among acutely, severely burned patients admitted to a burn unit in Koeln, Germany (Haum et al. 1995). Of 225 patients, 70 had positive BACs (greater than 0.01 percent). These 70 patients also had a significantly higher fatality rate (31.5 percent) compared with patients with negative blood alcohol levels (18.1 percent). Patients with BACs of 0.01 to 0.06 percent had a fatality rate of 17.4 percent, whereas patients with BACs greater than 0.06 percent had a fatality rate of 40.4 percent (figure 1). In addition, 59 patients were alcoholic; these patients spent more time in the intensive care unit and were more likely than patients with no history of alcoholism to die from their injuries (31 versus 18 percent, respectively). Similarly, Jones et al. (1991) showed that alcoholic burn victims had a mortality rate three times that of nonalcoholic burn victims and also died of smaller burns (measured as a percentage of total body surface area). Thus, both alcohol consumption and alcoholism appear to increase the risk for fatal burn injuries.

> *A review of five recent U.S. studies shows that between 33 and 61 percent of persons who died as a result of burns were drinking.*

Ballard et al. (1992) examined whether smoking and alcohol use interact to increase the risk of injury from residential fire. Their results indicated that the risk of fire injury in households with heavy drinkers (defined as those who consume five or more drinks per drinking occasion) was greater than that in households whose members consumed less alcohol. Although further analysis showed that heavy drinkers were at increased risk for injury in part because they tended to live in households with higher smoking levels, the authors suggested that the total number of drinks consumed per occasion may contribute to the cause of a fire or may affect the drinker's judgment, mobility, and ability to escape.

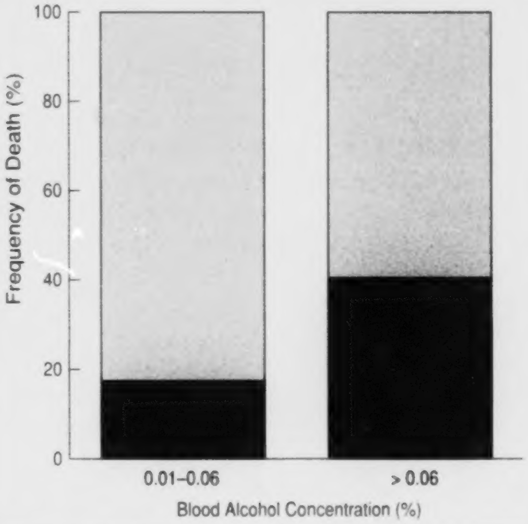
Water Safety

Drownings, including drowning related to boating mishaps, are the third most common cause of unintentional injury death for all ages (Baker et al. 1992). According to the U.S. Coast Guard (1992), recreational boating incidents result in more than 1,000 deaths each year.

Available evidence suggests that alcohol use may be a major risk factor for drownings and other fatal and nonfatal injuries that occur on or near the water (Howland et al. 1993; Perrine et al. 1994). In a statewide survey conducted in Massachusetts in 1990, 36 percent of male respondents and 11 percent of female respondents who had averaged 13 days on or near the water during the summer reported drinking the last time they had been on or near the water (Howland et al. 1993). Approximately one-third of the men who reported drinking consumed four or more drinks on that occasion. Analysis of data from 7 general population studies revealed that an average of 34 percent of 2,151 drownings had involved alcohol use (Hingson and Howland 1993).

Although empirical research identifying risk factors associated with boating injuries per se has not been extensive (Molberg et al. 1993), field tests have shown that alcohol affects an individual's ability to operate vessels and boating equipment. For example, tests conducted by the Coast Guard revealed that boat operators suffering from environmentally induced fatigue (from sun, wind, glare, and wave motion) were 10 times more likely to miss course correction signals if they also were legally intoxicated (Wright 1985).

Figure 1. Admission blood alcohol level and fatality rates among 225 burn patients.



	0.01–0.06	> 0.06
No. of survivors	147	28
No. of nonsurvivors	31	19

Source: Haum et al. 1995. Reprinted from *Burns*, 21(3), Haum, A.; Perbix, W.; Hack, H.J.; Stark, G.B.; Spilker, G.; and Doehn, M. Alcohol and drug abuse in burn injuries. Pages 194–199. Copyright 1995, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington 0X5 1GB, UK.

Alcohol also may induce physiologic changes that reduce the probability of survival in or near the water. These changes include hypothermia, which in turn may increase the risk of cardiovascular failure; increased susceptibility to inner ear equilibrium disturbances that result from rapid temperature changes and cause disorientation; weakened diving response; and inhibited blood-gas exchange (Howland et al. 1993).

Increasing evidence indicates that alcohol is a major risk factor for boating fatalities (Hingson and Howland 1993; Molberg et al. 1993). Data from the Boating Accident Report Files in Ohio for 1983 to 1986 indicate that alcohol consumption may have played a role in up to 21 percent of reported boating mishaps involving at least one fatality (Molberg et al. 1993). A study of drownings resulting from boating accidents in four States showed that 45 percent of the victims had positive BACs (at least 0.01 percent) and 22 percent were intoxicated (BAC of at least 0.10 percent) (Hoxie et al. 1988).

Boat passengers who drink alcohol also are at increased risk of injury regardless of the drinking behavior of the boat operator (Howland et al. 1993). Alcohol impairs balance and motor function. As a result, a drinking passenger could be at risk for falling overboard even if the boat is drifting or is being operated safely (Hingson and Howland 1993; Howland et al. 1993). In addition, the ability of alcohol to alter judgment also results in a greater chance that an intoxicated person will disregard guidelines for water safety; for example, by failing to wear a life vest or by swimming alone at night or in an unsupervised area (Hingson and Howland 1993).

In addition to its role in drownings and boating accidents, alcohol may contribute to diving accidents that result in spinal cord injury. One case-control study revealed that divers who sustained spinal cord injuries were about four times more likely to have consumed alcohol than were control subjects (Branche et al. 1991). A study by Perrine et al. (1994) showed that the ability of 13 male recreational divers to perform entry dives into shallow water was progressively and markedly impaired at BAC values of 0.04 percent and greater. Perhaps more disturbing, even at BAC values of up to about 0.12 percent, divers did not recognize that their diving performance was impaired or that their risk for injury was increased.

Air Traffic Safety

The suggestion that alcohol use by pilots may cause air traffic injuries is based on two primary findings: Alcohol impairs the ability of pilots to fly, and alcohol influences the ability of pilots to judge their own performance (Morrow et al. 1991).

Among major U.S. airlines, no fatal crash report has implicated alcohol use as the causative factor (Modell and Mountz 1990). However, a study of commuter airplane and air taxi crashes between 1983 and 1988 showed that of 126 fatally injured pilots, 3 tested positive for alcohol (BACs of 0.04, 0.16, and 0.17 percent). All of the tested pilots were flying air taxis rather than scheduled commuters (Baker and Lamb 1992).

Despite limited epidemiologic evidence for alcohol's role in airplane crashes, researchers have conducted extensive studies of alcohol's effects on flight performance in simulated flight experiments. Billings et al. (1991) found that BACs as low as 0.025 percent produced significant decrements, including planning, performance, and procedural errors and failures of vigilance. A similar study found that BAC values under 0.04 percent can result in pilot errors (Ross et al. 1992). In addition, alcohol may have hangover effects that compromise safety. Morrow et al. (1993) have shown that alcohol consumption resulting in BACs of 0.08 to 0.10 percent can impair pilots' performance on flight simulators as much as 8 hours later. These findings and those of others suggest that the 8-hour lag time between drinking and piloting required by the Federal Aviation Administration may need to be extended (Yesavage et al. 1994).

Age also has been implicated in the role of alcohol in air traffic crashes, but data on the interaction of pilot age and alcohol use are equivocal. Some studies indicate that older pilots are more affected by alcohol than young pilots; however, older pilots may more accurately assess their impaired performance and may be less confident in their ability to fly after drinking (Morrow et al. 1991). Other studies have failed to find age-related differences in responses to alcohol, such as recollection of previously learned tasks and susceptibility to acute or hangover effects of alcohol (Morrow et al. 1993; Yesavage et al. 1994).

The involvement of alcohol in fatal crashes during air or space transport has been examined among members of the U.S. Air Force (Stout et al. 1993). Data were collected from death certificates from 283 active duty members. The cause of death was analyzed using the Alcohol-Related Disease Impact software, which allows calculation of alcohol use, misuse, and disease in populations. The analysis revealed that 66 fatalities were alcohol related, 5 of which occurred in air or space transport accidents. Unfortunately, the impact of alcohol use on air traffic safety was not addressed further in this study.

The proposed association between use of alcohol by pilots and reduced aircraft safety must be viewed with caution because data are based on flight simulator studies and individual case studies, rather than epidemiologic studies. The absence of a well-established surveillance system means that information about alcohol use by pilots in general or those involved in nonfatal crashes is rarely available (Li 1994). For example, in the study of commuter and air taxi pilots mentioned earlier, although tests for alcohol or drugs had been performed in 86 percent of pilots who were killed in airplane crashes, only 18 percent of those who were seriously injured and 0.4 percent of those who were not injured were tested (Baker and Lamb 1992). Furthermore, although studies using flight simulators are important and informative, they cannot fully duplicate a "real life" situation, in that the risk of being in a crash involves the interaction of many factors that may not be easily duplicated in a laboratory environment (Li 1994).

Occupational Injuries

Researchers have recognized problems created by alcohol in the workplace since the 1940s, but the relationship between alcohol use and occupational injuries remains to be clarified (Stallones and Kraus 1993; Webb et al. 1994). Many studies have determined the proportion of workers in different jobs or job categories who use alcohol but have failed to extend the analysis further; that is, to examine the relationship between alcohol intake and job performance. Studies that have examined work injuries involving alcohol use find that the rates of these injuries vary extensively by industry. In general, however, data suggest that the percentage of alcohol-associated occupational injuries is low compared with other injuries (Cherpitel 1992). The available data suggest that approximately 4 percent of nonfatal occupational injuries involve alcohol use (Cherpitel 1993*a*; Stallones and Kraus 1993).

In reviewing epidemiologic studies of alcohol-related trauma, Cherpitel (1992) noted the paucity of data on alcohol-related work injuries relative to other alcohol-related injuries. Work regulations, policies, and norms restricting alcohol use on the job, combined with inconsistent testing for alcohol after occupational injuries or fatalities, limit the size of samples and therefore the reliability of the data and may thus preclude more comprehensive studies (Cherpitel 1992). The wide variation in hazards associated with machinery and equipment across different industries further complicates assessment of alcohol-related occupational injuries (Dawson 1994). However, a few studies have attempted to overcome some of these obstacles to better quantify the injury risk posed by alcohol use.

One such study has relied on data from the 1988 National Health Interview Survey (Dawson 1994). This study found that 7.2 percent of 29,192 employed adults surveyed had been involved in an on-the-job accident in the previous year. A higher rate, about 13 percent, was reported by those working as skilled or unskilled laborers or those engaged in strenuous job-related physical activity. Approximately 25 percent of the workers reported heavy drinking (defined as having consumed five or more drinks on at least one occasion) in the past year. As the frequency of heavy drinking increased, so did the risk for occupational injury, even after adjustment for demographic variables, occupation, and high physical demands of certain jobs: Odds ratios[2] ranged from 1.08 for one episode of heavy drinking during the past year to 1.74 for daily heavy drinking. These values likely underestimate the impact of alcohol use on work-related injuries because they include *all* episodes of drinking and do not measure the risk of being injured as a direct result of *working while intoxicated.* The data also indicated that even light to moderate drinking increased the likelihood of work injury.

An Australian study has examined alcohol's role in work-related fatal accidents (Hollo et al. 1993). Based on data from coroner reports for 1,737 persons who died from work injuries, 16 percent had measurable BACs; of these, 65 percent had a BAC of 0.05 percent. Most of the work-related fatalities associated with alcohol use occurred among tradesmen, production process workers, and laborers. Alcohol involvement also had a significant impact on the risk for fatal injuries among persons in administrative, executive, and managerial occupations.

The data also indicated that even light to moderate drinking increased the likelihood of work injury.

A smaller scale study of 454 municipal employees (excluding uniform fire and police officers) in a large U.S. city examined the relationship between work-related injury and substance use at work (including use of either or both alcohol and illicit drugs) (Holcom et al. 1993). Substance use at work was associated with occupational injury among persons in jobs categorized as high risk for injury (e.g., jobs involving operation or maintenance of heavy machinery or equipment or exposure to toxic or poisonous chemicals). No such association was found for persons in jobs categorized as low risk for injury (e.g., desk jobs).

The Role of Alcohol in Violence

Interpersonal violence increasingly has become a concern in the United States and internationally. Research findings have identified alcohol as a problem in a significant proportion of violent and aggressive events. Lenke (1990) has estimated that 50 percent of both victims and perpetrators of violence use alcohol; that this association occurs consistently across countries, demographic subgroups, and types of violence (e.g., homicides, suicides, and assaults) suggests that it is not an artifact.

Alcohol's presence in a violent event is often considered presumptive of a causal relationship. However, drinking proximal to such an event does not necessarily mean that alcohol affected the behavior of the persons involved. Moreover, alcohol is not by itself sufficient to account for violence but is likely to be only one of multiple factors that act in combination (Collins and Messerschmidt 1993). Findings from numerous studies implicate personality, expectancy, situational, and sociocultural factors that may interact with alcohol's physiologic effects, but whether and under what circumstances these interactions lead to violence remains unclear (Martin 1993).

Two main approaches are used to study the relationship between alcohol and violence (Pernanen 1993). The first is a fact-finding approach, used to determine the prevalence of alcohol-related violence and the statistical strength of the relationship under different conditions. For example, fact-finding approaches may examine the extent of alcohol involvement in violent episodes by either the perpetrator, the victim, or both; the relationship between the amount of alcohol consumed and increases or decreases in violent events; or the effects of sudden changes in alcohol availability on rates of violent crime (Pernanen 1993).

The second is an explanatory research approach, which attempts to identify mechanisms by which alcohol causes violence. Explanatory research approaches examine internal processes and external cues that may increase the risk of violence when alcohol is consumed. Internal processes include simple biological and psychodynamic impulses that may interact with alcohol to predispose a person to violence. External cues, such as situational factors, are thought to stimulate cognitive mechanisms that play a role in alcohol-related violence. These cognitive mechanisms may involve expectations of alcohol's effects or changes in perception and cognitive processing (i.e., cognitive impairment) that occur with alcohol consumption. Explanatory research approaches also may identify social and interactional dynamics that combine with cognitive effects of alcohol to precipitate violence. For example, cognitive effects of drinking may alter the drinker's perception and interpretation of interpersonal encounters. Explanatory research approaches can be used to complement fact-finding approaches (and vice versa) to provide answers about causal links between alcohol use and aggression (Pernanen 1993).

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[2] An odds ratio provides an indication of risk and is defined as the ratio of the odds of occurrence of one event to that of an alternative event. In this study, the odds ratio was defined as the odds of occupational injury among persons who drank five or more drinks on one or more drinking occasion to the odds of such injury among persons who never drank five or more drinks per drinking occasion.

Social and cultural contexts may play important roles in alcohol-associated violent events.

Social and cultural contexts may play important roles in alcohol-associated violent events (Parker 1993*b*). For example, poverty has been recognized as a strong correlate of homicide (Loftin and Hill 1974), and a recent study has demonstrated that alcohol consumption can heighten the impact of social problems, such as poverty, on violence (Parker 1993*a*). The study found that elevated levels of aggregate alcohol consumption create a context in which the relationship between poverty and homicide is intensified. Similar studies of situations and conditions in which alcohol and violence are linked may indicate whether alcohol increases violence in certain contexts and may help reveal risk factors for violence (Parker 1993*b*).

Investigations of alcohol and violence often examine relationships between alcohol consumption and violence as they occur in populations or in specific violent events. Investigations of alcohol's relationship to violence also may be experimental in nature, designed to determine the impact of alcohol on aggressive responses under controlled conditions to more closely scrutinize potential causative factors.

Alcohol and Violence in Populations and in Violent Incidents

Rates of alcohol consumption associated with violence vary with type of violence. Findings from recent studies of alcohol and violence, including studies of alcohol's role in homicides, suicide, and family and domestic violence, are discussed in the paragraphs that follow. Key findings from many of these studies are summarized in table 4.

General Studies

Pernanen (1991) investigated the alcohol-violence link by using data from interviews of a large representative sample of residents in a Canadian community and from police reports in that community over a 12-month period. He found that either the victim, the perpetrator, or both had been drinking in more than half of the most recent incidents of violence reported by respondents and in 42 percent of all violent crimes reported to the police (Pernanen 1991). Among interview respondents, 51 percent of perpetrators and 30 percent of victims had been drinking; among violent crimes, 31 percent of perpetrators and 26 percent of victims had been drinking. Thus, alcohol was involved not only in extreme cases of violence, as represented by violent crimes, but also in the more routine confrontations that occurred among community residents.

Pernanen's study also showed that risks for alcohol-related violence varied according to demographic factors. Young adults (aged 20 to 29) were at greater risk than persons of other ages, and young men were most at risk for alcohol-related violence. Alcohol involvement differed according to the gender of the assailant and the victim. For example, alcohol was present in 62 percent of episodes involving a male victim and assailant, in 53 percent of episodes involving a female victim and a male assailant, and in 27 percent of episodes involving a female assailant. In addition, alcohol involvement varied according to the relationship between the victim and the perpetrator, with the greatest proportion (78 percent) observed for violent episodes between strangers. Alcohol's role in such episodes is an important area for future research.

An investigation in England examined the role of alcohol in violent offenses among male convicts aged 17 to 21 years (Cookson 1992). This study found a clear association between alcohol use at the time of the offense and violent crime (Cookson 1992).

Relationships among drinking patterns, alcohol-related problems, and injuries due to violence have been studied in patients admitted to hospital ERs in Contra

Costa County, California (Cherpitel 1993*b*). Patients who were victims of violence were compared with patients with injuries not related to violence in terms of BACs, self-reported drinking patterns, and alcohol problems. Patients with injuries due to violence were more than twice as likely to have positive BACs (0.01 percent or greater). Furthermore, among males and females over age 30, those with injuries due to violence were more likely to report drinking before the injury event, frequent heavy drinking, consequences of drinking, experiences associated with alcohol dependence, and prior treatment for an alcohol problem.[3] One-half of patients with violence-related injuries reported drinking within 6 hours of the violent event. Of these patients, more than one-third reported having consumed seven or more drinks, and approximately two-thirds reported that less than 1 hour had elapsed between the time of their last drink and the violent event.

One study of the role of alcohol in suicide observed that nearly 36 percent of suicide victims had a positive BAC.

Homicide

Evidence suggests that alcohol involvement is common in homicide cases. In a review of 15 studies investigating the drinking patterns of homicide offenders, Murdoch et al. (1990) found that percentages of offenders who were drinking when they committed the crime ranged from 7 to 85 percent for all studies. In most of these studies, more than 60 percent of homicide offenders were drinking at the time of the offense. Pernanen's (1991) review of five studies found that between 36 and 70 percent of persons who committed homicides drank directly before the crime. Finally, in 500 cases of suspected homicide that occurred from 1959 to 1983 in Copenhagen, Denmark, 55 percent of the defendants were intoxicated at the time of the alleged homicide, and 55 percent were habitual users of alcohol, other drugs, or both (Gottlieb and Gabrielsen 1992).

Muscat and Huncharek (1991) studied the role of alcohol in adult domestic homicides involving firearms that occurred in Ohio from 1982 to 1985 by using data from police records, from the Ohio Department of Rehabilitation and Corrections, and from county medical examiners of six major cities. They found that alcohol was used by either the victim, the offender, or both in 73 percent of the homicides. Nearly 62 percent of offenders reported drinking on the day of the homicide. Among victims, 31 percent of females and 63 percent of males had BACs of 0.10 percent or greater. In a similar study conducted in Omaha, Nebraska, Clayton and Webb (1991) analyzed police records for the years 1975–1988 to determine alcohol's involvement in homicides. The data showed that 44.2 percent of homicide offenders and 33.6 percent of homicide victims were intoxicated at the time of the crime and that rates of alcohol involvement differed according to race and gender. For example, among homicide victims, blacks were more likely than whites to have consumed alcohol, and black females were more likely than black males to have consumed alcohol. Among victims of alcohol-related homicides, 98 percent of black victims and 94 percent of white victims were relatives or acquaintances of the perpetrator. The latter findings contrast with data from Pernanen (1991), which show that alcohol was less likely to be a factor in violent crimes involving acquaintances than in those involving strangers.

Suicide

Several studies have observed relationships between suicide and both alcohol use and alcoholism. One study of the role of alcohol in suicide observed that nearly 36 percent of suicide victims had a positive BAC (0.001 percent or greater) (Hayward et al. 1992). In addition, those who had been drinking before committing suicide were younger, more likely to be males, more likely to have used carbon monoxide poisoning, more likely to have experienced the breakup of a relationship, and less likely to have sought professional help before the suicide. Although the data did not provide evidence for a causal association between alcohol use and suicide, the authors suggested that for some people, alcohol may have contributed to the decision to commit suicide.

A second study examined drinking patterns and alcohol-related problems among patients admitted to a London hospital after attempting suicide by self-poisoning (Merrill et al. 1992). Nearly one-half of the patients reported drinking in the 12 hours preceding poison ingestion. Approximately 15 percent of the patients reported drinking amounts of alcohol that fell

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[3] In this study, frequent heavy drinking was defined as drinking once a week or more often and having five or more drinks at a sitting also once a week or more often.

Table 4. Summary of recent studies evaluating the association between alcohol consumption and violence.

Study	Region	Population	Measures	Findings
General Studies				
Cherpitel 1993*b*	Contra Costa County, California	Probability sample of emergency room patients (N = 1,770)	Interview BAC*	Patients with violence-related injuries were more likely than other patients to have consumed alcohol prior to the event, to use more alcohol, and to report other alcohol-related problems.
Cookson 1992	Great Britain	Random sample of convicted male criminal offenders aged 17–20 years (N = 604)	Interview	Alcohol use at the time of the offense was associated with violent offenses, and violent offenses were associated with excessive consumption of alcohol.
Pernanen 1991	Thunder Bay, Ontario, Canada	Probability sample of community residents (N = 933); all incoming police reports of violent crime during a 12-month period (N = 781)	Interviews with community residents; census of police reports	Among community residents, 51% of assailants and 30% of victims were drinking at the time of the event; 31% of perpetrators and 26% of victims of violent crimes were drinking at the time of the crime.
Homicides				
Clayton and Webb 1991	Omaha, Nebraska	All homicide police records for 1975 to 1988 (N = 416)	Information on alcohol use by victim and offender	At the time of the crime, 44.2% of offenders and 35.6% of victims were intoxicated; alcohol consumption prior to homicide was more likely among acquaintance homicides.
Gottlieb and Gabrielsen 1992	Copenhagen, Denmark	Suspected homicide cases 1959–1983 (psychiatric reports were available for 251 defendants from a total of 500 homicide cases)	Psychiatric assessments of homicide suspects	When the crime was committed, 55% of the 251 defendants were intoxicated (with alcohol or other drugs). Substance abusers were 30 times more likely than non-abusers to commit a homicide.
Muscat and Huncharek 1991	Ohio	Adult primary domestic homicides involving firearms that occurred from 1982 to 1985, using data from police records, the Ohio Department of Rehabilitation and Correction, and medical examiners (N = 129)	Interview with offenders BAC	On the day of the homicide, 61.7% of offenders reported consuming alcohol. Alcohol was used by the victim, the offender, or both in 73% of cases.

*BAC = blood alcohol concentration.

into a high-consumption category.[4] Thirty-four percent of men and 15.5 percent of women had alcohol-related problems (e.g., alcohol dependence, social problems, or physical illness related to alcohol use). The incidence of alcohol misuse among these patients was greater than that observed in other studies of attempted suicide, perhaps because this study obtained more detailed information on alcohol histories than is generally available in other studies (Merrill et al. 1992).

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[4] In this study, the high-consumption category was defined as drinking greater than 50 units per week for men and greater than 35 units per week for women, where 1 unit represents 8 grams of alcohol as found in a half-pint of beer, a standard glass of wine, or a single measure of spirits.

Table 4. Summary of recent studies evaluating the association between alcohol consumption and violence *(continued)*.

Study	Region	Population	Measures	Findings
		Suicides		
Duberstein et al. 1993	Monroe County, New York	Random sample of suicides among persons aged 21 years and older since 1988 (N = 94, 67% participation rate)	Interview with first-degree relatives about 7 weeks after the suicide	Alcohol abuse when combined with other major life stressors (e.g., divorce, conflicts, or arguments) may increase the risk of suicide.
Hayward et al. 1992	Western Australia	Consecutive suicides occurring from 1986 to 1988 (N = 515)	BAC at the time of death; additional information collected from police, doctor, and family	Some alcohol use was associated with 35.8% of suicides. Moderate to significant intoxication was associated with 24.5% of suicides. Alcohol use was highest among suicides involving carbon monoxide poisoning.
King et al. 1993	Michigan	Female patients aged 13–19 years hospitalized for various psychiatric disturbances (N = 54)	Self-report survey	Alcohol consumption combined with perceived family dysfunction predicted severity of suicidal behavior. Among girls with major depression, alcohol consumption was associated with severity of suicidal behavior.
Merrill et al. 1992	United Kingdom	Patients admitted to a hospital for deliberate self-poisoning (N = 250)	Interview	Drinking within 2 hours prior to poisoning was reported by 46.4% of patients; 34% of men and 15.5% of women had alcohol-related problems.

Research has suggested that suicide associated with alcoholism and alcohol dependence, in contrast to suicide associated with depression, may be preceded more often by interpersonal loss and conflict (Duberstein et al. 1993). When suicide victims who had a diagnosis of alcohol or substance dependence (A/SD) were compared with those with anxiety and mood disorders (M/AD), a substantially larger proportion of victims with A/SD had experienced interpersonal stressors, including disruptions of personal relationships (e.g., divorce and separation) and conflicts or arguments with coworkers or family members, within 6 weeks of their suicide. The authors suggested that persons with A/SD may experience a broader range of interpersonal stressors than do persons with M/AD and that these findings are consistent with a causal relationship between such stressors and suicide in alcohol or other drug abusers (Duberstein et al. 1993).

King et al. (1993) have studied alcohol consumption in relation to depression severity and family dysfunction as predictors of suicidal behavior in a small sample of adolescent girls (aged 13 to 18) hospitalized for various psychiatric disturbances. Alcohol consumption was found to combine with perceived family dysfunction to predict the severity of suicidal behavior as assessed on a clinician-completed behavior scale. Among girls who had a diagnosis of major depression, alcohol consumption alone was significantly associated with the severity of suicidal behavior in the 6 months before the study. The researchers suggested that alcohol consumption may increase the likelihood of suicidal behavior among some psychiatrically disturbed girls, perhaps through its effects on judgment, mood, and impulsive behavior.

Family and Domestic Violence

Alcohol is present in a substantial proportion of domestic violence incidents. Alcohol represents a significant risk factor for husband-to-wife violence (Collins and Messerschmidt 1993), and an estimated 30 percent of child abuse cases may involve alcohol (Murdoch et al. 1990). The study by Pernanen (1991) cited earlier found that of the approximately 450 accounts of the most recent violent episode reported by community residents, 20 percent involved marital abuse. In these marital incidents, 44 percent of assailants and 14 percent of victims had been drinking. A study of men charged with battering their partners found that 60 percent of the batterers were under the influence of alcohol at the time of the incident; approximately 70 percent of batterers were under the influence of alcohol, other drugs, or both (Roberts 1988).

Research indicates that women with alcohol problems experience high rates of violence both during childhood and as adults, suggesting that being the victim of violence may affect a woman's use of alcohol and that alcohol problems may in turn increase the risk of violent victimization (Miller and Downs 1993). In a study that compared women in alcoholism treatment programs with women in the general population, in other treatment centers (i.e., mental health centers and shelters for partner violence), and in drinking and driving classes, Miller and Downs (1993) found that women undergoing treatment for alcoholism experienced higher rates of childhood victimization, more severe violence by fathers, and more childhood sexual abuse than did those in the general population or in drinking and driving classes. Women undergoing treatment for alcoholism also experienced more childhood sexual abuse than did women without alcohol problems in other treatment centers and higher levels of violence by partners than did women in the general population. These findings illustrate the complexity of determining causal links between alcohol and violence. They confirm correlations between alcohol and domestic violence and suggest that domestic violence also may perpetuate alcohol abuse.

Alcohol represents a significant risk factor for husband-to-wife violence, and an estimated 30 percent of child abuse cases may involve alcohol.

Although all of the above studies show clear associations between alcohol use or abuse and violence, the results should be interpreted with caution. Many studies in this field suffer from methodological limitations. For example, they may use small sample sizes or convenience samples (e.g., incarcerated offenders) that are not representative of all violent offenders or their drinking patterns. In many studies, information on the order in which drinking and violence occur may be incomplete or nonexistent, and in studies relying on self-reports, levels of alcohol consumption may be underreported or overreported (Collins and Messerschmidt 1993; Martin 1992; Murdoch et al. 1990). Furthermore, causal associations between alcohol and violence are far from understood. An important challenge of future studies will be to distinguish occasions when alcohol contributes to violence from those in which its presence is coincidental and irrelevant (Collins and Messerschmidt 1993).

Experimental Studies of Alcohol and Aggression

Alcohol may directly affect psychological mechanisms that in turn increase the likelihood of aggressive behavior (see Pihl and Peterson 1993 for a review). These mechanisms can be studied in the laboratory, where contributing variables can be carefully selected and controlled. Experimental studies typically involve individuals whose responses are examined in the absence or presence of alcohol or placebo. One common approach employs the Buss-Taylor task, a timed competitive task, in which the intensity and duration of an electric shock administered by one experimental subject to another, presumed subject (actually a computer) are used as a measure of aggression. Additional neuropsychological and behavioral tests may be used alone or in combination with the Buss-Taylor task to assess relationships between alcohol and aggression.

Various mechanisms have been proposed as factors in alcohol-induced aggression. For example, researchers have theorized that alcohol may contribute to aggression by increasing sensitivity to pain and that alcohol may impair problem-solving strategies through effects on functions of the brain's frontal lobe (Pihl and Peterson 1993). Pain, as defined broadly to include frustration and absence of expected rewards, is the most apparent stimulus for aggression. Thus, an alcohol-induced increase in pain sensitivity would be an attractive explanatory factor for alcohol-associated aggressive behavior. Although alcohol is known to have anesthetic properties, one investigator has noted increased subjective ratings of sensitivity to electric shocks by persons given alcohol relative to persons given a placebo (Gustafson 1986) and that intoxicated persons exposed to a frustrating event experience stronger frustration and react with more aggression than sober subjects exposed to the same event (Gustafson 1986).

Two recent studies have examined the effects of alcohol on frontal lobe function in relation to aggressive behavior. In the first study, a series of neuropsychological tests were administered to individuals who received alcohol or a placebo (Peterson et al. 1990). This study showed that alcohol had little influence on intellectual abilities but affected performance on tasks associated with assessment, planning and foresight, organizational behavior, and other functions associated with the frontal cortex. Based on their results and suggestions from other reports that frontal lobe functioning is critical for formulating verbal and motor strategies needed to manage novel or threatening situations (Luriia 1980; Peterson and Pihl 1990), the investigators proposed that alcohol may interfere with mechanisms needed to deal with such situations (Peterson et al. 1990).

> *Several investigators have suggested that drinking, risk taking, and sensation seeking may be part of a broader personality style of behavioral undercontrol.*

A second study went further to determine how alcohol affected performance on an aggression task as well as on tests of frontal lobe functioning (Lau et al. 1992). Results showed that after provocation, individuals who scored low on tests of frontal lobe functioning were more aggressive when sober than those with intact functioning, indicating a fundamental impairment in the former group that may contribute to aggressive behavior. In addition, after ingesting an intoxicating dose of alcohol, individuals with intact frontal lobe functioning were as aggressive as their lower functioning counterparts. This finding supports the theory that alcohol may alter frontal lobe function to increase the likelihood of an aggressive response to provocation (Pihl and Peterson 1993).

These and other experimental studies have provided some of the most direct evidence for a causal role of alcohol in aggression. Results from such studies may have important implications for preventing alcohol-associated aggression. Increased knowledge of contributing factors may lead to methods for treating people who may be more prone to alcohol-instigated aggression or for teaching people how to avoid violent responses when drinking (Taylor 1993).

Risk-Taking Behavior

Research indicates that drinking is associated with risk-taking and sensation-seeking behavior among adolescents and adults (Zuckerman 1979). For example, one study has reported that adolescents who drank heavily engaged more frequently in high-risk activities, such as swimming alone or taking another person's medication (Windle et al. 1992). Among adults admitted to a trauma unit for alcohol-related injuries, three-fourths admitted that they regularly failed to use seat belts (Brotman et al. 1995). Several investigators have suggested that drinking, risk taking, and sensation seeking may be part of a broader personality style of behavioral undercontrol (Cox 1987; Windle 1990). People with such traits may be more likely to participate in various alcohol-related risky behaviors, such as drinking and driving and unprotected sexual activity.

Among the many serious consequences of high-risk behavior are injury or death due to trauma or disease. Although numerous studies have established links between alcohol and injury and between alcohol and risk taking, the association of alcohol and risk taking with injury has received little attention until recently. Cherpitel (1993*d*) has examined this association among 1,150 persons aged 18 years or older admitted for ER treatment. Twelve percent of the sample reported receiving medical treatment for an injury. These people were less likely to be abstainers and more likely to report moderate and heavy drinking compared with those with no injuries. Injured persons also were more likely to be male and younger (aged 18 to 29). Risk perception, risk taking, impulsivity, and sensation seeking were positively associated with injury and with quantity and frequency of drinking. A direct association was observed between the quantity and frequency of drinking and the likelihood of injury, but the association was significant only for males. There was no evidence for an interaction of alcohol use and dispositional variables with injury. Thus, although the results corroborate those of other studies that show links between alcohol use and injury, this study found that personality traits associated with risk taking and sensation seeking have little effect on the occurrence of injury when alcohol consumption is considered. One possible explanation for this finding is that the study considered all types and causes of injury rather than focusing on certain causes of injury (e.g., traffic crashes) that may be associated with risk-taking and sensation-seeking behavior. In addition, relationships between risk taking and alcohol consumption may be affected by cultural differences in definitions of alcohol use situations and by differences in expectations of alcohol's effects in drinking situations.

Binge drinking may be associated with high-risk and unconventional behaviors and is common among high school and college students (Kann et al. 1993; Valois et al. 1995; Wechsler et al. 1994). In a large sample of high school students surveyed in South Carolina, a high frequency of binge drinking was reported, especially among white males (47.5 percent) and white females (33.3 pecent) (Valois et al. 1995). Black males and females showed comparatively lower levels of binge drinking (23 percent and 16.2 percent, respectively). Associations were observed between alcohol use and carrying a weapon among white males, black males, and black females; between alcohol use and fighting among white females; and between binge drinking and fighting among white males.

Among adolescents, the frequency of drinking and driving has been correlated with speeding, driving after use of alcohol or illicit drugs, and taking risks in traffic.

In a national survey of college students at 140 4-year colleges in the United States, 44 percent of students reported binge drinking (defined as drinking 5 or more drinks per occasion for men and 4 or more drinks per occasion for women) (Wechsler et al. 1994). Nineteen percent reported frequent binge drinking (defined as binge drinking on at least three occasions during the 2 weeks preceding the survey). Frequent binge drinkers were 7 to 10 times more likely than nonbinge drinkers to get into trouble with campus police, damage property, sustain injury, or have unplanned or unprotected sex (table 5). For example, among frequent binge drinkers, 35 percent of males and 9 percent of females reported damaging property; 16 percent of males and 6 percent of females reported confrontations by campus police. Binge drinkers also reported significantly higher frequencies of dangerous driving behaviors than nonbinge drinkers.

Binge drinkers not only place themselves at risk for negative consequences but also may create problems for others. In the study discussed above, college students who were not binge drinkers at schools with middle to high levels of binge drinking were more likely than students at schools with lower levels of binge drinking to experience problems as a result of other students' drinking. These problems included being pushed, hit, or assaulted; experiencing unwanted sexual advances; being insulted; having arguments; or having property damaged (Wechsler et al. 1994).

Drinking and Driving

Risky driving behaviors that increase the likelihood of traffic crashes are well documented. They include drinking and driving, using drugs and driving, speeding, passing at intersections, proceeding through yellow lights, and making sudden lane changes (Donovan 1993). Among adolescents, the frequency of drinking and driving has been correlated with speeding, driving after use of alcohol or illicit drugs, and taking risks in traffic.

Risky driving behavior is more prevalent among younger than older drivers (Jonah and Dawson 1987; Peck 1985). Recently, a statewide survey of licensed drivers aged 18 to 25 years was conducted in Colorado to assess behavioral and psychosocial correlates of drinking and driving in this group (Donovan 1993). The survey showed that drinking and driving was related to a variety of risky driving practices, such as violating traffic laws and driving after illicit drug use, and to the level of involvement in other problem behaviors, such as problem drinking,[5] other drug use, and delinquent-type behavior.[6] Drinking and driving also was related to certain psychosocial characteristics, including hostility, aggression, and a tendency toward social unconventionality and risk taking. Taken together, these findings suggest that drinking and driving may be part of a larger "lifestyle" of problem behavior in young adulthood. The author also suggested that driving after drinking may be prevalent in this group because

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[5] In this study, problem drinking was determined by using an 11-item scale to assess frequency of drunkenness in the past 6 months, frequency of high-volume drinking (5 or more drinks per occasion) in the past 6 months, and number of negative personal and social consequences due to drinking in the past 6 months.

[6] Delinquent-type behavior was determined by using scales that assessed the frequency of shoplifting and other types of theft, the frequency of lying, and the frequency of starting fights or arguments or purposely damaging others' property.

Table 5. Risk of alcohol-related problems among college-age students.

Reporting Problem*	Nonbinge Drinkers, Percent (N = 6,894)	Infrequent Binge Drinkers		Frequent Binge Drinkers	
		Percent (N = 4,090)	Adjusted OR (95% CI)†	Percent (N = 3,291)	Adjusted OR (95% CI)‡
Have a hangover	30	75	6.28 (5.73–6.87)	90	17.62 (15.50–20.04)
Do something you regret	14	37	3.31 (3.00–3.64)	63	8.98 (8.11–9.95)
Miss a class	8	30	4.66 (4.15–5.24)	61	16.58 (14.73–18.65)
Forget where you were or what you did	8	26	3.62 (3.22–4.06)	54	11.23 (10.05–12.65)
Get behind in schoolwork	6	21	3.70 (3.26–4.20)	46	11.43 (10.09–12.94)
Argue with friends	8	22	3.06 (2.72–3.46)	42	7.77 (6.90–8.74)
Engage in unplanned sexual activity	8	20	2.78 (2.46–3.13)	41	7.17 (6.37–8.06)
Get hurt or injured	2	9	3.65 (3.01–4.43)	23	10.43 (8.70–12.52)
Damage property	2	8	3.09 (2.53–3.77)	22	9.48 (7.86–11.43)
Not use protection when having sex	4	10	2.90 (2.45–3.42)	22	7.11 (6.07–8.34)
Get into trouble with campus or local police	1	4	2.50 (1.92–3.26)	11	6.92 (5.44–8.81)
Require medical treatment of alcohol overdose	<1	<1	NS	1	2.81 (1.39–5.68)
Have five or more alcohol-related problems since the beginning of the school year§	3	14	4.95 (4.17–5.89)	47	25.10 (21.30–29.58)

*Problem occurred not at all or one or more times. Chi-square comparisons of nonbinge drinkers, infrequent binge drinkers, and frequent binge drinkers and each of the problems are significant at $p < 0.001$, except for alcohol overdose ($p = 0.002$). Sample sizes vary slightly for each problem because of missing values. OR indicates odds ratio; CI indicates confidence interval. Nonbinge drinkers were students who consumed alcohol in the past year but did not binge. Infrequent binge drinkers were students who binged one or two times in a 2-week period. Frequent binge drinkers were students who binged three or more times in a 2-week period.

†Adjusted ORs of infrequent binge drinkers vs. nonbinge drinkers are significant at $p < 0.001$.

‡Adjusted ORs of frequent binge drinkers vs. nonbinge drinkers are significant at $p < 0.001$, except for alcohol overdose, $p < 0.01$.

§Excludes hangover and includes driving after drinking as one of the problems.

Source: Wechsler et al. 1994. Reprinted by permission. *Journal of the American Medical Association* 272 (21):1675, 1994. Copyright 1992–94, American Medical Association.

drinking, especially in public places or at friends' homes, is such a large part of the social lives of young adults (Donovan 1993).

In a survey of students in grades 9 through 12 in 50 States and the District of Columbia, Escobedo et al. (1995) examined the problem behaviors of drinking and driving, frequent alcohol use, other drug use, and binge drinking (defined as consumption of five or more drinks consecutively). Survey data revealed that the prevalence of drinking and driving increased substantially with the frequency of alcohol use and binge drinking. The prevalence of drinking and driving also increased with the number of years elapsed since students first began to use alcohol and was higher among students who used alcohol and other drugs than among students who used alcohol only. These findings suggest the need for prevention efforts that target underage drinking, such as strategies that address the ease with which adolescents obtain alcohol, in reducing drinking and driving and associated motor vehicle crashes among young people.

A study of persons considered to be at high risk for drinking and driving has examined causal factors associated with driving behaviors (Yu and Williford 1993*a*). Respondents included people who were in alcoholism treatment centers, drinking driver programs, and county jails and on probation. The study found that people who were prone to risk and sensation-seeking behaviors in general tended to engage in risky driving behaviors (e.g., speeding and driving through stop signs). Chronological age was a significant predictor of risky driving: The younger the individual, the greater the likelihood of risk taking in general and high-risk driving in particular. Furthermore, initiation of alcohol use at an early age and the drinking behaviors of respondents' fathers had an impact on risk- and sensation-seeking attitudes, which in turn heightened risky driving. These findings show that high-risk driving may be, in part, a function of risk- and sensation-seeking attitudes that are formed early in life (Yu and Williford 1993*a*).

High-Risk Sexual Behavior

Drinking may affect sexual behavior because of expectations that men and women associate with alcohol, such as the belief that alcohol enhances sexual performance and decreases the nervousness associated with sexual performance (George and Norris 1991; Goldman and Roehrich 1991; Jessor and Jessor 1977; Norris 1994). For both men and women, the likelihood of engaging in sexual activity after drinking, especially after heavy drinking (i.e., eight or more drinks), is higher than the likelihood after light or moderate drinking and is higher still when the encounter involves a new rather than an established partner (Norris 1994; Stinson et al. 1992). Alcohol has long been considered a sexual disinhibitor and, as such, may increase the risk for unwanted pregnancy and infection with human immunodeficiency virus (HIV) (the virus that causes acquired immunodeficiency disease, or AIDS) and other infectious agents that cause sexually transmitted diseases (STDs) (Norris 1994; Stinson et al. 1992; Wilsnack 1991). The volume of literature describing the relationship between alcohol use and risky sexual behavior, particularly as it relates to exposure to HIV, has increased steadily in recent years.

> *Drinking may affect sexual behavior because of expectations that men and women associate with alcohol, such as the belief that alcohol enhances sexual performance and decreases the nervousness associated with sexual performance.*

Condoms can protect against infection and pregnancy, but many individuals who know this continue to engage in unprotected sexual activities (Stinson et al. 1992). Several studies have shown that alcohol use is associated with unprotected sexual intercourse in various populations, including adolescents, college students, and homosexual men (Cooper et al. 1994; McCusker et al. 1990; Strunin and Hingson 1993; Wechsler et al. 1994). However, the mechanisms by which alcohol may reduce the likelihood of condom use or safer sexual practices have not been delineated empirically.

Adolescents and Young Adults

A primary concern associated with high-risk sexual behavior of adolescents is the dormant nature of the AIDS virus (Cooper et al. 1994). The Centers for Disease Control (1991) estimates that fewer than 1 percent of AIDS cases occur in adolescents, whereas persons in their twenties account for 20 percent of all cases. Because the incubation period between exposure to HIV and the onset of symptoms associated with AIDS can be as long as 10 years, the disproportionate number of cases seen among persons in their twenties may be, for many, a consequence of infection during the teen years. Thus, research has focused on identifying individual and situational factors (such as alcohol) associated with sexual risk-taking behaviors that lead to HIV exposure (Leigh and Morrison 1991).

Numerous studies have shown that adolescents are more likely to engage in unprotected sex when they drink alcohol than when they do not (Biglan et al. 1990; Cooper et al. 1994; Ford and Norris 1994; Gillmore et al. 1992; Keller et al. 1991; Koopman et al. 1994; Kraft et al. 1990; Rolf et al. 1990–91; Strunin and Hingson 1992). For example, a study by Strunin and Hingson (1992) has addressed the influence of drinking on sexual activity and condom use among adolescents. Their study included 1,152 adolescents living in Massachusetts who were 16 to 19 years of age identified through a random-digit dial telephone survey. Sixty-six percent of the sample reported having had sexual intercourse. Of these sexually active young people, 64 percent reported having had sex after drinking, and 49 percent said they were more likely to have sex if they and their partner had been drinking. However, only 37 percent reported that they always used condoms, and 17 percent reported using condoms less often after drinking. The authors suggested that because so few adolescents consistently used condoms, the greatest risk of unwanted pregnancy and infection with HIV and other agents that cause STDs was probably associated with the increased likelihood of having sex after drinking, not the decreased likelihood of condom use after drinking.

Ford and Norris (1994) surveyed young (aged 15 to 24) African Americans and Hispanics living in low-income areas of Detroit regarding alcohol and marijuana use and unprotected sexual intercourse. The survey revealed that when sexual partners drank or smoked marijuana together, the consistency of condom use was decreased (Ford and Norris 1994). This association held even when effects of other variables related to sexual risk-taking were taken into account; however, the impact of alcohol and marijuana use varied widely across different gender and ethnic subgroups. In addition, alcohol use had a greater negative effect on condom use for Hispanic males than for other groups.

A recent study of 1,259 sexually active adolescents aged 13 to 19 years found that 73 percent of adolescents who had ever consumed alcohol were sexually experienced, whereas 41 percent of adolescents who had never consumed alcohol were sexually experienced (Cooper et al. 1994). In addition, the study observed that alcohol and other drug use were associated with increased sexual risk-taking[7] on the occasions of first intercourse ever and first intercourse with the most recent partner. These associations held even after demographic, personality, and experiential factors (e.g., age, race or ethnicity, age at first intercourse, degree of religious convictions, level of thrill and adventure seeking, and lifetime alcohol and drug use) were controlled for. In addition, alcohol use was more common and appeared to be more strongly associated with sexual risk-taking among white adolescents than among black adolescents.

Adults

Associations have been observed between alcohol use and high-risk sexual behaviors, such as failure to use condoms or engage in safer sex practices, in both heterosexual adults (Bagnall et al. 1990; Ericksen and Trocki 1992; Fitterling et al. 1993; Trocki and Leigh 1991) and homosexual men (Leigh 1990; McCusker et al. 1990; Paul et al. 1993; Penkower et al. 1991; Stall et al. 1990; Trocki and Leigh 1991). Data from the 1988 National Health Interview Survey have been used to examine the impact of alcohol dependence or abuse on risk for infection with HIV among persons aged 18 years or older (Stinson et al. 1992). Analysis showed that individuals who met diagnostic criteria for alcohol dependence or abuse, who engaged in heavier drinking (consumption of approximately two drinks per day), or who consumed at least nine drinks on one occasion at least once in the year preceding the survey were at a much higher risk of exposure to HIV and of developing AIDS than were abstainers or drinkers who consumed less alcohol (Stinson et al. 1992). A gender difference in risk for AIDS also was observed but only for people who reported consuming at least nine drinks per occasion at least once in the previous year: In that drinking category, the risk for women was greater than for men.

Studies of alcohol use and risky sex among homosexual men indicate that these men are more likely to engage in high-risk sexual practices when drinking than when sober (Leigh 1990; McCusker et al. 1990; Paul et al. 1993; Penkower et al. 1991; Stall et al. 1990; Trocki and Leigh 1991). Furthermore, limiting alcohol use appears to have positive effects, in that homosexual men who reduced their alcohol consumption were significantly more likely to stop unsafe sexual practices than were those who maintained or increased their alcohol consumption (McCusker et al. 1990).

Penkower et al. (1991) have examined the risk for HIV infection in relation to a variety of behavior, health, and psychosocial factors among homosexual and bisexual men. The researchers found that among men who reported having engaged in anal intercourse in the previous 6 months, heavy drinking, moderate to heavy drug use, and younger age increased the risk of infection. These factors also were associated with increased numbers of sexual partners, anonymous sex, and failure to use condoms.

A similar study has investigated the prevalence of HIV infection and risk behaviors among 425 homosexual and bisexual men aged 17 to 22 years who frequented public venues in San Francisco and Berkeley, California (Lemp et al. 1994). Approximately 9 percent of the men sampled were HIV positive; of these, 70 percent were unaware that they were infected. One-third of the study participants reported having had unprotected anal intercourse in the 6 months before the survey, and being under the influence of alcohol or nitrites during sex was one of several predictors of unprotected anal intercourse. However, the data did not indicate whether substance use leading to impaired judgment or disinhibition was a causal factor in high-risk sexual activity.

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[7] In this study, sexual risk-taking was determined based on responses to questions about the use of condoms, discussion or failure to discuss risks associated with unprotected sex before intercourse, and the degree of partner intimacy (i.e., how well respondents knew their partners).

Some investigations have found no relationship between drinking and sexual risk-taking for homosexual men (Bolton et al. 1992; Martin and Hasin 1991; Ostrow et al. 1990; Temple and Leigh 1992; Trocki and Leigh 1991; Weatherburn et al. 1993) or heterosexual men (Leigh 1990; Temple and Leigh 1992; Trocki and Leigh 1991). Inconsistencies in study findings may be caused in part by variations in the recruitment of study participants (Paul et al. 1991); for example, studies of persons recruited from bars may overestimate the prevalence of alcohol and other drug use. In addition, most studies of interactions between alcohol and high-risk sexual behavior have focused on white, middle class individuals. Thus, knowledge of the drinking practices and sexual activities of homosexuals and of heterosexuals in ethnic minority groups is limited.

Summary

Each year, more than 100,000 deaths in the United States result from alcohol-related causes. Alcohol use and abuse can influence a variety of behaviors with potentially serious consequences for people of all ages and backgrounds. Alcohol use has been linked with a substantial proportion of fatalities and deaths resulting from traffic crashes, falls, fires, and drownings. In addition, alcohol has been associated with high-risk sexual behavior and is thought to play a significant role in many instances of interpersonal violence.

Alcohol and injury may interact in two ways. First, the context and place in which alcohol is consumed may contribute to an increased risk for injury. For example, consuming alcohol in bars where the risk of assault may be high increases drinkers' exposure to hazardous circumstances. Second, alcohol may contribute to injury through direct biological effects on perception and responsiveness to potential hazards, such as road hazards encountered by drivers.

Traffic crashes are the leading cause of death for Americans under age 35, and alcohol use plays a role in a significant proportion of these deaths. However, alcohol-related traffic crashes have declined in recent years. For example, the number of intoxicated drivers decreased by 28 percent between 1983 and 1993, and the number of intoxicated drivers aged 16 to 24 decreased by nearly 50 percent over the same period. The decline in injuries due to alcohol-related traffic crashes among young people may be attributable, in part, to recent legislation raising the minimum drinking age to 21. Between 1977 and 1983, the number of male drivers involved in fatal alcohol-related crashes has dropped, but the number of female drivers involved in such incidents has increased. Nevertheless, the number of female drivers involved in fatal alcohol-related traffic crashes remains well below that of males.

The direct involvement of alcohol use in other types of injuries, such as those resulting from airplane crashes, drownings or boating accidents, and violence is less clear. For example, alcohol use by pilots has been linked to reduced aircraft safety, but these findings are based largely on individual case studies, and epidemiologic data to show such associations are scarce. Simulated flight experiments, however, clearly demonstrate that alcohol consumption can interfere with pilot performance and may thereby increase the risk of air traffic injuries and fatalities.

Accumulating evidence links alcohol use with accidents that occur on or near the water. Epidemiologic studies showing a high prevalence of positive BACs among victims of drownings and boating accidents indicate that alcohol use is an important risk factor in such mishaps. Studies have shown that drinking can increase the risk of injury or death for boat operators as well as boat passengers—because alcohol impairs balance and motor function, a drinking passenger may be at risk for falling overboard even when the boat is being operated safely. Alcohol involvement also has been demonstrated in a large proportion of diving accidents that result in spinal cord injury.

In addition, alcohol use may contribute to the risk of injury or death resulting from fires or burns, perhaps because alcohol may reduce awareness of fire alarms and smoke and because alcohol may increase the likelihood of falling asleep while smoking. Moreover, drinking may affect the outcome of burn injuries, as shown in studies that demonstrate higher fatality rates among burn patients with positive BACs compared with burn patients with no detectable blood alcohol.

Numerous studies have shown that alcohol is a factor in a significant proportion of violent events. Strong relationships have been observed between alcohol and various types of violence, including homicides, suicides, and spousal abuse. For example, a review of investigations examining the link between alcohol and homicide found that, in most studies, more than 60 percent of persons who committed homicides were drinking at the time of the offense. In addition, drinking may increase the risk of being a victim of violence and of sustaining injury in a violent situation. One study has shown that ER patients injured in violent events were more likely to have positive BACs than were ER patients with injuries unrelated to violence. It should be noted, however, that alcohol's presence in a violent event does not indicate that the drug caused that event. Rather, alcohol is likely to be only one of many elements that act in combination to precipitate violence in some individuals.

Finally, alcohol may play an important role in risk-taking or sensation-seeking behaviors. Of great concern is the relationship between alcohol use and high-risk sexual behavior that has been established in studies of both adolescents and adults. Alcohol has disinhibiting effects that may increase the likelihood of unsafe sexual activities which may facilitate the spread of AIDS or other STDs. In addition, recent findings have shown that alcohol dependence and alcohol abuse are associated with an increased risk of becoming infected with HIV and of developing AIDS.

As for other causes of injury and death, the causal role of alcohol in high-risk sexual behavior is unclear. The relative paucity of information about alcohol's direct role in adverse consequences resulting from high-risk behaviors, violence, falls, drownings, and other types of accidents, combined with the tremendous impact these consequences have for society, underscores the need for further research and improved methods for assessing causal relationships between alcohol consumption and alcohol-related casualties.

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Chapter 8

Economic Aspects of Alcohol Use and Alcohol-Related Problems

Introduction

This chapter explores two major areas in which economic research has improved our understanding of alcohol consumption and alcohol-related problems. The first area is made up of the factors that determine the demand for alcoholic beverages and contribute to problems that are associated with alcohol consumption. Principal focal points in this area of research are the critical role of prices and taxes and the possible role of alcohol advertising as determinants of alcohol consumption and alcohol problems. The chapter also considers how the economic welfare of individuals is affected by policies that work through their effect on the demand for alcoholic beverages.

The second area is the effect of alcohol consumption and alcohol problems on labor market behavior and productivity. Recent estimates suggest that roughly two-thirds of the economic costs of alcohol use and misuse may take the form of lost or reduced productivity, broadly defined (Rice 1993; Rice et al. 1990). Various measures of productivity, such as wages, earnings, income, and employment, are considered. The distinction between using the level of alcohol consumption and various indicators of alcohol abuse or dependence as variables in analyses of the determinants of productivity is an issue of particular concern.

The discussion presented here is based primarily on the recent economics literature. The *Eighth Special Report to the U.S. Congress on Alcohol and Health* reviews some earlier research that touches on several of the issues discussed here and surveys some complementary economic issues that are not addressed in this chapter. In addition, discussion of some topics having important economic dimensions appears elsewhere in this Special Report. Discussion of the societal impacts or costs of alcohol abuse, as well as some economic aspects of treatment for alcohol problems, is found in Chapter 10, Treatment of Alcoholism and Related Problems. The implications for drinking-related problems of prevention-oriented availability policies other than taxes or prices are considered in Chapter 9, Prevention of Alcohol Problems.

Finally, for readers interested in pursuing economic topics in alcohol research in greater detail, several useful recent surveys might be consulted: Cook (1991) provides a general overview of economic aspects of alcohol-related problems; Chaloupka (1992), Cook and Moore (1993*c*), Grossman (1989), Grossman et al. (1993, 1994), Laixuthai and Chaloupka (1993), and Leung and Phelps (1993) survey various economic aspects of tax and price policy; Grossman (1993) examines economic aspects of addictive behavior; Saffer (1993*b*, 1995) considers economic aspects of alcohol advertising; and Mullahy (1993) assesses the economic aspects of the consequences of drinking and alcohol-related problems on labor market productivity.

Demand for Alcohol and Drinking-Related Problems

Alcohol Demand, Prices, and Taxes

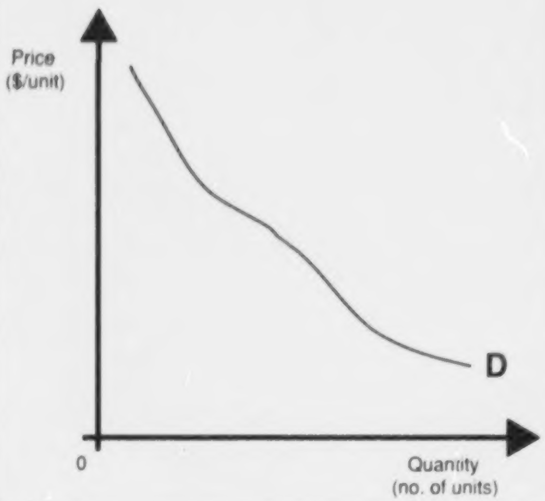
Conceptual and Methodological Issues

Economists conceive of the *demand* for a particular good[1] as a functional relationship between the quantity of the good that consumers are willing and able to purchase and the price of the good, the prices of other related goods, consumers' income or purchasing power, and various other factors. A basic hypothesis concerning the demand for any good is that an increase in the price of the good leads to a decrease in the quantity demanded. This hypothesis of downward-sloping demand curves (in quantity-price space, as shown in figure 1) is so widely maintained and has accumulated such broad empirical support that it is often referred to as the "Law of Demand."

A substantial body of research has examined the role of prices as a determinant of alcohol consumption and alcohol-related problems. Economists measure the responsiveness of consumption to changes in price (other things held constant) by calculating the "price elasticity of demand." Formally, the price elasticity of demand is defined as the percentage change in quantity demanded divided by the percentage change in price that caused the change in demand. In brief, if a change in price of X percent generates a change in quantity demanded of Y percent (other things held constant), then the price elasticity of demand is defined as Y÷X.[2]

Several features of the elasticity measure are worth noting. First, for most goods, the price elasticity of demand is a negative number. The negativity of price elasticity reflects the law of demand; that is, a price increase (a positive change) leads to a decrease in quantity demanded (a negative change), and the converse.

Figure 1. A typical demand curve.



Second, economists classify demand for different goods as "elastic" or "inelastic" according to whether the change in quantity demanded is proportionately larger or proportionately smaller than the change in price. If the quantity demanded is sensitive to price changes to the extent that a given price increase calls forth a proportionately larger reduction in quantity demanded, then demand is termed "elastic" and the value of the elasticity is less than -1 (e.g., -2). In this case, an increase in price reduces the total expenditure on the good in question because of the relatively large decline in the quantity demanded. In contrast, if the quantity demanded is relatively unresponsive to changes in price so that a given price increase elicits a proportionately smaller decrease in quantity demanded, then the demand is termed "inelastic" and the value of the elasticity is between 0 and -1. In the case of a good with inelastic demand, price increases lead to increases in consumers' spending on the good. The extreme case of a demand relationship that is completely unresponsive to changes in price is referred to as "perfectly inelastic" demand and corresponds to an elasticity value of zero.

Third, the price elasticity of demand is affected by the narrowness of the definition of the good in question and by the availability (and price) of close substitutes. Narrowly defined goods tend to have more elastic demand than do broadly defined product categories. For example, the quantity demanded of a particular brand of beer might fall sharply (reflecting a highly elastic demand) in response to a 20-percent price increase on that specific product (other things held constant) as consumers substitute other brands of beer that had not increased in price. However, the quantity demanded of beer in general probably would fall by a smaller proportion in response to a 20-percent increase in all beer prices, suggesting that the demand for the category "beer" is less elastic than the demand for a particular component of the category.[3] Thus, comparing estimates of elasticity for different product categories requires caution.

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[1] A "good" can be a product, commodity, or service–anything of value that can be bought and sold.

[2] A simple demand function may be represented mathematically as $Q = f(P)$, where Q is the quantity purchased, P is the price, and $f(\cdot)$ is the functional relationship expressing how quantity demanded depends on price. The elasticity is expressed as $(\Delta Q/Q) \div (\Delta P/P)$, which can be rearranged as $(\Delta Q/\Delta P) \cdot (P/Q)$. This formula shows that elasticity is related to, but is not the same as, the slope of the demand function.

Fourth, the demand for an alcoholic beverage represents the demand for all the attributes associated with that beverage, not just the alcohol content. Although some consumers may be concerned primarily with alcohol content in their purchasing and consumption decisions, many consumers consider a variety of other characteristics and culturally determined factors as well. The fact that alcohol content is not the only consideration in consumers' decisionmaking is supported by the limited degree of substitution between beer, wine, and distilled spirits found in empirical studies.

Finally, the demand for any good (and the corresponding elasticity) may change in response to factors that affect people's tastes or the prices of other goods. As a result, elasticity estimates should be viewed as "snapshots" of a dynamic process, not once-and-for-all measures of a static property.

Examination of the role of price as a determinant of the demand for alcoholic beverages is often motivated by interest in alcohol taxes. Special taxes that apply specifically to alcoholic beverages are levied by the Federal Government, the governments of each of the 50 States and the District of Columbia, and some local governments. (Table 1 shows excise tax rates that applied to beer, wine, and distilled spirits as of December 1994. Sales taxes imposed by State and local governments are in addition to the taxes shown here.)

Although the intention of legislators is normally to generate government revenue, alcohol taxes, through their effect on prices, may affect alcohol consumption levels and related public health outcomes. The relationship between alcohol taxes and alcohol prices has not been widely investigated (see, however, Culbertson and Bradford 1991 and Sass and Saurman 1993), but there is a clear presumption that higher taxes are correlated with higher prices, in both longitudinal and cross-sectional terms. That is, one expects that tax increases on one or more alcoholic beverages will lead to price increases for the same beverages, and that alcoholic beverages will command a higher final price in States that impose higher alcohol excise taxes.

The existence of this qualitative relationship (higher taxes lead to higher prices) says little about the quantitative aspects of the tax-price linkage, which may be illustrated by the question, "By how much will the price of beer be affected by a 10-percent increase in the Federal beer excise tax?" The answer relates to the issue of tax *incidence*: Who bears the final burden of the tax (not necessarily the person from whom the tax is collected)? For example, imposing a tax of $.10 per loaf of bread might cause the price of bread to rise by $.07 per loaf. In this case, 70 percent of the tax is borne by consumers in the form of higher prices paid, and 30 percent is borne by sellers in the form of lower (net) prices received. That the price change might differ from the tax change is the result of the interacting forces of demand and supply, which in turn reflect the behavior of buyers and sellers, who are both seeking to maximize their own satisfaction or profits. Other things being equal, consumers generally bear a larger share of the incidence of an excise tax the more inelastic the demand for the taxed good.

The demand for a particular good may depend on a variety of factors in addition to the price of the good, including consumers' incomes and the prices of related goods (substitutes and complements). Economists use various elasticity constructs to measure the sensitivity of the quantity demanded to changes in any one factor. The income elasticity of demand, for example, is the ratio of the percentage change in quantity demanded to the percentage change in income that caused demand to change. For *normal* goods, consumption rises as income rises, and so the income elasticity assumes a positive value. However, *inferior* goods are defined as goods whose consumption decreases in response to rising income. An example of an inferior good might be generic beer, which consumers could forgo in favor of a brand-name alternative as their incomes rise. For normal

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[3] This issue alludes to technical concerns as well. For example, how does one measure percentage changes in the price of beer, when beer is a category with dozens of individual brands and package sizes? The issue becomes even clearer when considering the demand for a broader category such as "alcoholic beverages." In practice, prices (and quantities) of these composite goods are measured using index numbers. The Consumer Price Index includes categories for beer, wine, distilled spirits, and alcoholic beverages.

Table 1. Federal and State excise tax rates per gallon on alcoholic beverages, December 1994.

	Beer	Table Wine	Distilled Spirits
FEDERAL	$0.58	$1.07	$13.50[1]
Alabama	$0.53	$1.70	(*)
Alaska	$0.35	$0.85	$ 5.60
Arizona	$0.16	$0.84	$ 3.00
Arkansas	$0.23	$0.75	$ 2.50
California	$0.20	$0.20	$ 3.30
Colorado	$0.08	$0.32	$ 3.28
Connecticut	$0.19	$0.60	$ 4.50
Delaware	$0.16	$0.97	$ 5.46
District of Columbia	$0.09	$0.30	$ 1.50
Florida	$0.48	$2.25	$ 6.50
Georgia	$0.48	$1.51	$ 3.79
Hawaii	$0.89	$1.30	$ 5.75
Idaho	$0.15	$0.45	(*)
Illinois	$0.07	$0.23	$ 2.00
Indiana	$0.12	$0.47	$ 2.68
Iowa	$0.19	$1.75	(*)
Kansas	$0.18	$0.30	$ 2.50
Kentucky	$0.08	$0.50	$ 1.92
Louisiana	$0.32	$0.11	$ 2.50
Maine	$0.35	$0.60	(*)
Maryland	$0.09	$0.40	$ 1.50
Massachusetts	$0.11	$0.55	$ 4.05
Michigan	$0.20	$0.51	(*)
Minnesota	$0.15	$0.30	$ 5.03
Mississippi	$0.43	$0.35	(*)
Missouri	$0.06	$0.36	$ 2.00
Montana	$0.14	$1.06	(*)
Nebraska	$0.23	$0.75	$ 3.00
Nevada	$0.09	$0.40	$ 2.05
New Hampshire	$0.30	(*)	(*)
New Jersey	$0.12	$0.70	$ 4.40
New Mexico	$0.41	$1.70	$ 6.06
New York	$0.21	$0.19	$ 6.44
North Carolina	$0.53	$0.79	(*)
North Dakota	$0.16	$0.50	$ 2.50
Ohio	$0.18	$0.32	(*)
Oklahoma	$0.40	$0.72	$ 5.56
Oregon	$0.08	$0.67	(*)
Pennsylvania	$0.08	18%	(*)
Rhode Island	$0.10	$0.60	$ 3.75
South Carolina	$0.77	$1.15	$ 2.72
South Dakota	$0.27	$0.93	$ 3.93
Tennessee	$0.13	$1.10	$ 4.00
Texas	$0.20	$0.20	$ 2.40
Utah	$0.35	13%	(*)
Vermont	$0.27	$0.55	(*)
Virginia	$0.26	$1.51	(*)
Washington	$0.19	$0.87	(*)
West Virginia	$0.18	$1.00	(*)
Wisconsin	$0.06	$0.25	$ 3.25
Wyoming	$0.02	$0.28	(*)

[1] Federal excise taxes on distilled spirits are $13.50 per *proof* gallon. A proof gallon is the amount of liquid that contains one-half gallon of pure alcohol.

(*) Wholesale and/or retail sales are controlled by government in these States. Prices are set by governments according to various mark-up formulas, so no single excise tax rate exists.

Source: Distilled Spirits Council of the United States 1994.

goods, values of the income elasticity that exceed 1 are sometimes associated with *luxury* goods, whereas goods with income elasticity between 0 and 1 are termed *necessities*.

The influences of the prices of related goods are captured in *cross-price elasticities*. Goods that are *substitutes* for one another exhibit positive cross-price elasticity values (as the price of one good increases, demand for a substitute increases). Goods that are *complements* for one another exhibit negative cross-price elasticity values. Cross-price elasticity values were found to be important in a recent study that examined the case for equalizing excise taxes per unit of alcohol content on beer, wine, and distilled spirits (Saffer and Chaloupka 1994). The authors found that the greater the degree of substitutability among beverages, the stronger is the case for increasing taxes on beer and wine relative to taxes on distilled spirits.

Thus, although related, prices and taxes must be considered separately. Economic theory suggests that the "full price" faced by consumers is the relevant determinant of consumer behavior. Whether a high full price results from a low pretax price and high taxes or a high pretax price and low taxes is an important consideration for revenue officers but not for consumers. The high cross-sectional correlation of excise taxes and prices is one reason why many empirical studies directly examine tax effects rather than price effects; the unavailability of suitable price data is another reason.

Using tax variables as proxies for price variables in studies of consumer behavior can cause problems. If State-level excise tax rates are correlated with other characteristics that help to determine individuals' propensities to use or misuse alcohol (e.g., regional customs or traditions, religious or cultural orientations), statistical estimates of the influence of taxes (or prices) may be biased unless controls for these factors are included. For example, if excise taxes are highest in States where drinking is relatively low for cultural reasons, a spurious negative relationship between taxes and drinking results. (See Coate and Grossman 1988 and Chaloupka et al. 1993 for a discussion of the implications of statistical controls for these effects.)

Unlike some other countries, in this Nation the merits or shortcomings of alcohol excise tax policy are often assessed without considering the implications of such policies for consumer expenditures on alcohol (Walsh 1980). If the demand for alcoholic beverages is relatively

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insensitive to its price (price-inelastic), increases in alcoholic beverage prices induced by higher taxes will result in greater expenditures on alcoholic beverages and, therefore, lower aggregate expenditures on all commodities other than alcohol. Whether such reductions in other expenditures have important implications for the well-being of individuals and families (e.g., do expenditures on food or shelter decline in such instances?) is an area that has not been carefully investigated but may be an important welfare consideration for low-income subpopulations.

Finally, although much of the literature has examined the potential public health benefits from higher prices or taxes for alcoholic beverages (see Grossman 1989 and Grossman et al. 1994 for overviews), from an economic perspective such benefits come at a cost. Higher prices for alcoholic beverages affect all consumers of these products, whether or not their drinking imposes any adverse consequences on themselves or others. This point was made most compellingly by Pogue and Sgontz (1989), who observed that although higher prices may reduce alcohol consumption levels among alcohol abusers, they are likely to reduce consumption levels among more moderate drinkers as well. In short, moderate drinkers would suffer a loss in well-being due to their reduced consumption and the higher prices they pay for alcoholic beverages. Pogue and Sgontz's analysis, and an extension of their approach by Saffer and Chaloupka (1994), balances the social benefits of alcohol taxes (decreases in abusive consumption) against the economic burden that such taxes impose on moderate drinkers and alcohol abusers alike. Both studies conclude that substantial increases in taxes on alcoholic beverage taxes are justified. (For additional discussion of some welfare economics aspects of tax and price policy, see Kenkel 1993*a,b,c*; Manning et al. 1989, 1991; Phelps 1988; and Saffer and Chaloupka 1994.)

Although higher prices may reduce alcohol consumption levels among alcohol abusers, they are likely to reduce consumption levels among more moderate drinkers as well.

Effectively interpreting empirical studies of the price sensitivity of demand for alcoholic beverages is not completely straightforward. First, in studies of the factors that affect the consumption of alcoholic beverages, the definition of the alcohol consumption variable is critical. Studies of the effects of price changes on alcohol consumption have employed such disparate measures as the aggregate annual "apparent consumption" of beer, wine, and distilled spirits at the State level, based on State tax data (Chaloupka et al. 1993; Nelson 1990); responses to survey questions about actual alcohol consumption over a short period (e.g., 2 weeks) preceding the survey (Cook and Moore 1993*a*; Gao et al. 1995; Yen 1994); responses to survey questions about the number of "drinking occasions" or "heavy drinking occasions" in the last year (Kenkel 1993*b*, 1996; Manning et al. 1995); and diary-based reports of expenditures on alcoholic beverages (Atkinson et al. 1990; Heien and Pompelli 1989). Second, observations may be identical in terms of a particular consumption measure but still conceal important differences. For example, 2 individuals may each consume the same volume of alcohol over a 2-week period, but 1 has 1 or 2 drinks with dinner each evening, and the other has 10 drinks in 4 hours every Saturday night. These two individuals face different sets of risks from their alcohol consumption, but these differences cannot be addressed in a study that relies on, for example, 2-week alcohol consumption as its consumption variable. Thus, different consumption measures reflect different aspects of drinking behavior, and no single measure captures all the dimensions of alcohol consumption.

There also may be problems with the raw data. A substantial body of literature has considered the validity and reliability of self-reported alcohol consumption in surveys (see Midanik 1988 and Sobell and Sobell 1990 for reviews). Comparisons of representative survey data with aggregate sales data indicate that self-reported consumption levels tend to understate actual consumption, in one reported case by 60 percent (Manning et al. 1991). However, if reporting errors are random and bear no systematic relation to other variables in a study, the statistical results will be largely unaffected by underreporting. But to the extent that reporting errors are correlated with drinking levels and other relevant variables, statistical estimates may be biased (i.e., estimated parameter values may differ systematically from their true values), and inferences based on such estimates may be misleading.

Because the relationships between reporting errors and other variables, such as individual characteristics, are not well understood, it is not clear how best to mitigate the resulting biases in statistical estimates. For example, the severity of errors in self-reported consumption may depend on the way the survey is administered (see Hoyt and Chaloupka 1994 for a discussion), but knowing this does not indicate how to adjust for these effects. Using alternatives to self-reported consumption data, such as expenditures on alcoholic beverages (Atkinson et al. 1990), may introduce a different set of errors and biases. For example, expenditure data may also be subject to underreporting. Even if reported accurately, expenditures simply represent the product of price and quantity purchased; because prices vary widely both within and across beverage categories (Treno et al. 1993), high expenditure levels may result from larger levels of consumption of lower priced alcoholic beverages or smaller levels of consumption of relatively higher priced products. In summary, there is a need for research that provides a better understanding of the nature of reporting biases for alcohol consumption and of the relationship between brand choices and product quality.

Consumption of alcoholic beverages obeys the economic law of demand; that is, higher prices are associated with smaller levels of consumption.

Recent Empirical Research

A recent survey by Leung and Phelps (1993) provides a comprehensive overview of the empirical research on the demand for alcoholic beverages and its relationships to prices and taxes; the following discussion draws heavily on that survey.

A useful distinction may be drawn between studies that have obtained their results on the basis of aggregate consumption data (time-series data, cross-State data, cross-country data, and combinations thereof) and studies based on individual observations on consumption (typically cross-sectional data, which may also have a longitudinal component). To date, the literature shows considerably more findings from aggregate data studies than from individual data studies.

Whether the results are based on aggregate or individual-level data sources, however, a general consensus emerges from the empirical work undertaken so far: Consumption of alcoholic beverages obeys the economic law of demand; that is, higher prices are associated with smaller levels of consumption (holding constant other relevant determinants of demand such as income). The findings of negative associations hold for all three beverage types—beer, wine, and distilled spirits—as well as for cases where total alcohol consumption is the outcome under study. In the many studies surveyed by Leung and Phelps, a positive association between price and consumption appears in only a few instances.

Confirmation of the applicability of the law of demand is clearly important if economic analysis of alcohol consumption behavior is to be sensible. Yet, for most policy purposes, the important question is not so much "whether" but rather "how much." Thus, attention focuses not only on the sign of the estimated price elasticity but also on its magnitude.

Studies that have based their analyses on aggregate data have generally found that price elasticities of demand for alcoholic beverages are in the "inelastic" range. As summarized by Leung and Phelps, most studies of the price elasticity of demand for beer have found very inelastic price responsiveness (i.e., between -0.5 and 0). These studies include, Adrian and Ferguson (1987) (for domestic beer), Clements and Johnson (1983), Jones (1989), Ornstein and Hanssens (1985), Schweitzer et al. (1983), Selvanathan (1988), and Tsolakis et al. (1983). Some other studies have estimated larger, though still price-inelastic demands for beer (Adrian and Ferguson 1987 [for imported beer]; Nelson 1990; Thom 1984). In a few instances, analysts have estimated the price elasticity of demand for beer to be less than -1.0 and thus in the price-elastic range (Godfrey 1988; Uri 1986).

Estimates of price elasticities of demand for wine and for spirits obtained in these and other aggregate data studies have generally tended to cluster around values that are somewhat more elastic than the corresponding beer elasticity estimates. Most of the estimates of the price elasticity of demand for spirits summarized and reported by Leung and Phelps are in the range of -1.0 to -0.5 (Adrian and Ferguson 1987 [for imported spirits]; Clements and Johnson 1983; Godfrey 1988; Jones 1989; Nelson 1990; Ornstein and Hanssens 1985; Selvanathan 1988). Many of the estimates of the price elasticity of demand for wine are in the range of -2.0 to -0.5 (Adrian and Ferguson 1987; Duffy 1983; Jones 1989; Nelson 1990; Thom 1984; Tsolakis et al. 1983 [long-run model]; Uri 1986).

As the findings surveyed by Leung and Phelps show, price elasticity estimates may vary significantly from one study to another. Elasticity estimates obtained in more recent research have continued to exhibit substantial variation.

Lee and Tremblay (1992) used a sample of 31 annual U.S. time-series observations at the national level to investigate the demand for beer, with particular attention to the role of advertising (see the later discussion of advertising issues). Several different regression models were examined, and prices exhibited statistically significant negative influences on consumption in each case. Price elasticity estimates ranged from -0.46 to -0.81 in various specifications.

In a study similar to that of Lee and Tremblay in terms of questions addressed and data employed, Nelson and Moran (1995) used four related modeling approaches to examine the interrelated demands for beer, wine, and distilled spirits in the United States, with particular attention to the role of advertising. They found that demand was quite inelastic for each beverage, with estimated price elasticity for beer ranging from -0.37 to -0.45, wine from -0.18 to -0.38, and spirits from -0.58 to -0.63. The estimated elasticities were statistically significant in all four cases for beer and for spirits but in only two of four cases for wine. Average estimated income elasticities were 0.73 for beer, 1.02 for wine, and 1.31 for spirits. This study also provided estimates of the cross-price elasticities of demand (i.e., the effect of changes in the price of one beverage category on the demand for another beverage category) and concluded that the demands for the different alcoholic beverage categories were related only weakly to one another. All of the estimated cross-price elasticities were positive, but they were small (none as large as 0.2) and significant in only one-third of the cases. The most consistent significant finding was that beer and spirits were substitutes, but the estimated magnitudes were in the range of just 0.03 to 0.05. The greatest estimated cross-price elasticities were for the effect of beer prices on the demand for wine (0.19 was the largest), but these effects were statistically insignificant in every case.

Price elasticity estimates may vary significantly from one study to another.

Baltagi and Griffin (1995) used pooled time-series, cross-sectional data at the State level for 1960–1982 to analyze determinants of the demand for distilled spirits. Using a regression model that included liquor prices, prices in adjacent States, income, and past consumption as explanatory variables, they considered a number of estimation strategies. Price was a statistically significant influence in most specifications; the estimated price elasticity of demand varied from -0.64 to -2.25 depending on the estimation approach employed. The authors' preferred approach produced an estimate for the long-run price elasticity of demand of -0.69 but an insignificant estimate for income elasticity.

The study by Selvanathan (1992) used country-level aggregate data from nine industrialized countries (Australia, Canada, Finland, Japan, New Zealand, Norway, Sweden, the United Kingdom, and the United States) to estimate price and income elasticities for beer, wine, and spirits for each country. Although most of the estimated price elasticities were not statistically significantly different from 0, 26 of the 27 point estimates of elasticity (3 beverages times 9 countries) were negative. The United States had the most inelastic demands, with estimated elasticities of -0.11, -0.05, and -0.11 for beer, wine, and spirits, respectively. Estimated income elasticities for the United States were all positive and were significantly larger for spirits (1.36) than for beer and wine (0.71 and 0.63, respectively). An important conclusion of the Selvanathan intercountry study was that the parameters of alcoholic beverage demand differ significantly from one country to another, so that it is inappropriate to estimate a single demand function for alcoholic beverages for an assortment of countries.

A recent study by Goel and Morey (1995) examined the relationship between the demand for distilled spirits and the demand for cigarettes. Using pooled time-series, cross-sectional data on alcohol and cigarette consumption at the State level for 1959–1982, the authors estimated a simultaneous system of two demand equations. The effect of liquor price on liquor demand was negative and significant, but the estimated elasticity was only -0.13 to -0.15 in alternative specifications. In contrast, the estimated income elasticity of demand for liquor, which was also significant, had a magnitude of +0.88 to +0.92. However, the most interesting findings were that cigarette demand and liquor demand were strongly linked and that the two products were substitutes in consumption. When the price of liquor rose, consumption of cigarettes increased, and when the price of cigarettes rose, consumption of liquor increased. Accordingly, an increase in the excise tax rate on liquor might yield a larger increase in net tax revenue than would be expected, as tax monies from additional cigarettes purchased because of the substitution effect from the higher price for liquor should be considered. Similarly, an increase in cigarette excise taxes might lead to increased liquor consumption and thus increased revenue from excise taxes on distilled spirits.

The recent literature has included a number of empirical findings on the effects of taxation or price based on individual-level survey data. Leung and Phelps (1993) provided a comprehensive survey of the important findings from this body of research; some selected estimates are summarized in table 2.

The general finding in this relatively small literature is that demand for alcoholic beverages is responsive to price. Indeed, the range of price elasticity estimates from these individual-data studies suggests somewhat greater price elasticity than do the aggregate-data studies discussed earlier.

Several studies have appeared since the 1993 publication of the survey by Leung and Phelps. Some of the most recent studies have considered novel aspects of the demand for alcoholic beverages but have also provided further confirmation that the demand is sensitive to changes in prices.

A recent study by Yen (1994) employs household-level reports of at-home consumption of alcoholic beverages from the 1987–1988 Nationwide Food Consumption Survey in a model that separates the decision of *whether* to consume alcoholic beverages from the decision of *how much* to consume. The dependent variable is the composite quantity of alcoholic beverages reported to have been consumed in the previous week. Price data were constructed based on reported expenditures for each category of alcoholic beverages, and the study controlled for income, price of nonalcoholic beverages, household size and composition, and various regional and sociodemographic factors. Price had a statistically insignificant effect on the probability that alcoholic beverages were consumed, but it was highly significant in the decision of how much to consume; the estimated price elasticity of demand for alcoholic beverages was -0.34. The estimated income elasticity for the probability of consumption was modest (+0.37) but highly significant; for quantity of consumption, it was statistically indistinguishable from zero.

A recent study by Gao et al. (1995) used individual-level data from the same U.S. Department of Agriculture survey employed by Yen (1994) to obtain household level data. Gao et al. estimated a system of separate demand equations for the alcohol content of beer, wine, and distilled spirits. Based on these "converted quantity" measures, estimated elasticities were -0.22 for beer, -0.70 for wine, and -0.32 for distilled spirits. The wine elasticity result was statistically significant, but the findings for beer and distilled spirits were only marginally so. Estimates of income elasticity were large and significant for wine and distilled spirits (+5.03 and +1.21, respectively), but the income elasticity estimate for beer was slightly negative (-0.09) and only marginally significant.

Table 2. Summary of selected price elasticity estimates from individual data studies.

Study	Alcohol Use Measure and Price Elasticity Estimate
Heien and Pompelli (1989)	-.84 (beer consumption) -.09 (spirits consumption) -.21 (wine consumption)
Coate and Grossman (1988)	-.53 (youth beer consumption frequency 4–7 times per week) -.48 (youth beer consumption frequency 1–3 times per week) -.20 (youth beer consumption frequency less than once per week)
Grossman et al. (1987)	- 1.54 (youth beer drinking participation) - 3.29 (youth beer consumption frequency daily) - 4.07 (youth spirits drinking participation)
Kenkel (1993*b*)	-.48 (males' heavy drinking) -.58 (young males' heavy drinking) - 1.07 (females' heavy drinking) - 2.89 (young females' heavy drinking)
Atkinson et al. (1990)	-1.4 to -1.1 (alcohol expenditures of drinkers)

Source: Adapted from Leung and Phelps 1993.

As discussed in greater detail later, Cook and Moore (1993*a*) attempted to determine empirically whether youthful drinking behavior affects educational outcomes. A component of this study, which was based on a sample of young adults drawn from the National Longitudinal Survey of Youth, examined how youthful drinking behaviors depend on the price of alcoholic beverages, as measured in proxy form by the State-level excise tax on beer. Cook and Moore found negative and statistically significant relationships between the beer tax and three drinking measures: drinks per week, propensity to drink frequently, and propensity to be drunk frequently.

A key question is the extent to which heavy drinking, as distinct from the average level of alcohol consumption, responds to changes in the prices of alcoholic beverages. A recent study by Manning et al. (1995) used data on 18,844 people from the 1983 National Health Interview Survey (NHIS) to address this question by examining the extent to which price sensitivity varied across the spectrum from light to heavy drinkers. Using a statistical technique called quantile regression, Manning et al. estimated price elasticity values for subsets of drinkers grouped by consumption levels (this approach contrasts with standard regression models that seek to identify the average responsiveness to price across the study population). The study also examined the role of price in the separate decisions of whether to drink and, if yes, how much to drink, as well as the choice of whether to engage in heavy drinking (defined as the consumption of five or more drinks on a single occasion).

Manning et al. (1995) found a negative and statistically significant relationship between price and alcohol consumption for all consumers considered together, with an estimated price elasticity of -0.80. Decomposing this effect into the separate components of whether to drink and how much to drink, Manning et al. found a significant effect of price on the decision of whether to drink at all, but, among those who were drinkers, an insignificant effect of price on the choice of how much to drink. Further disaggregation of the effect of price on the consumption decisions of people grouped according to drinking levels revealed significant differences in the price sensitivity of light, moderate, and heavy drinkers. Quantile regression results (combining the probability of consumption and level of consumption aspects) indicated that the most price-sensitive drinkers were those at the median of the distribution of alcohol consumption (the 50th percentile); their estimated price elasticity was -1.19. Significantly less elastic demands were observed at either end of the distribution, and transitions were fairly smooth through the intermediate ranges. The lightest-drinking 5 percent of drinkers exhibited a price elasticity of -0.56, and sensitivity to price increased gradually up to the median of the consumption distribution. Above the median, price sensitivity declined. For the 90th percentile of consumption, the estimated price elasticity of -0.49 was significantly different from 0 and from the price elasticity estimated for drinkers at the 50th percentile. For the 95th percentile, the estimated price elasticity was slightly positive (0.12) but not significantly different from 0 (these results are summarized in table 3). The authors also found that income elasticity was positive and significant throughout the distribution of drinkers, with a high of 0.30 at the 80th percentile and modest decreases toward the tails of the distribution. Finally, they found that the probability of having any days of heavy drinking (five drinks or more) was negatively and significantly related to alcohol prices, with an elasticity of -0.58, but the effect of price on the number of such days was not significant.

Table 3. Summary of key results from Manning et al. 1995.

Alcohol Consumption Quantile (among drinkers)	Price Elasticity of Demand for Alcohol (point estimate)
0.05	-0.56
0.10	-0.53
0.20	-0.76
0.30	-0.90
0.40	-0.98
0.50	-1.19
0.60	-1.15
0.70	-0.96
0.80	-0.74
0.90	-0.49
0.95	+.12

Kenkel (1993*b*) examined the effects of prices and various policy measures on the frequency of heavy drinking and drunk driving. Using individual-level survey data from the Health Promotion and Disease Prevention supplement to the 1985 NHIS, Kenkel found that higher alcohol prices were associated with significant reductions in the frequency of heavy drinking (defined for this study as five or more drinks in a day) for males of all ages, for females of all ages, and for females aged 21 and below. However, the estimated effect was not statistically significant (although still negative) for males aged 21 and below.

A new analysis by Kenkel (1996) also examined the extent to which price effects on consumption differ between moderate and heavy drinkers. Using the same 1985 data set as employed in his earlier (1993*b*) study, Kenkel classified drinkers according to whether they reported having consumed five or more drinks in a day at any time in the past year. Those who met this criterion for heavy drinking were grouped according to their knowledge of three specific health problems associated with heavy drinking (throat cancer, liver cirrhosis, and cancer of the mouth). Kenkel examined the effect of price on both the frequency and the intensity of moderate drinking (defined for this study as up to four drinks in a day) and on the frequency of heavy drinking (intensity data were unavailable) for individuals with different levels of knowledge about the health risks of heavy drinking. Results for males and females were reported separately and appear in table 4.

For both males and females, Kenkel's demand analysis found differences between the price responsiveness of moderate and heavy drinkers. Perhaps more surprising, price effects on the frequency of heavy drinking varied greatly by knowledge of the health consequences of heavy drinking; those who knew that throat cancer, liver cirrhosis, and mouth cancer are all consequences of heavy drinking were much more responsive to price changes than were their less informed counterparts. The frequency of heavy drinking among the least well informed heavy drinkers exhibited no statistically significant price responsiveness. Kenkel suggested that this group, consisting primarily of very heavy drinkers, may be alcoholics with demands that are extremely insensitive to price; their reported ignorance of specific health effects could be considered an aspect of the denial of adverse consequences, a phenomenon that is frequently associated with alcoholism.

The studies by Manning et al. and Kenkel provide further confirmation that the demand for alcoholic beverages is sensitive to price. These studies also provide the first direct evidence of differences in the price responsiveness of drinkers at different levels of consumption. The conclusion that the heaviest-drinking 5 percent of drinkers (who report about four or more standard drinks per day) and ill-informed heavy drinkers are not sensitive to price changes may temper enthusiasm for policies aimed at reducing alcohol abuse by increasing prices. This is particularly true in light of the greater responsiveness of drinkers in the more moderate consumption ranges. However, the significant price elasticity estimates for drinkers up to the 90th percentile (with self-reported average consumption approaching three standard drinks per day) and for all but the least well informed heavy drinkers suggest that a range of problems related to alcohol may be affected by policies that influence price. The next section reviews research examining the more direct links between alcohol taxes and alcohol-related problems.

The conclusion supported overwhelmingly by the demand studies reviewed here is that the demand for alcoholic beverages is affected by price changes in the same way as are the demands for other products: Higher prices are associated with lower consumption levels. However, the research still exhibits substantial variation in measurement of the sensitivity of beverage demand to price changes. Most studies have found that the demand for beer is less responsive to price than are the demands

Table 4. Price elasticity estimates by drinker category from Kenkel 1996.

Category of Drinking	Price Elasticity, Males	Price Elasticity, Females	Price Elasticity Weighted Average
Frequency of moderate drinking	-0.928	-1.025	
Intensity of moderate drinking	-0.509	-0.750	
Total moderate drinking	-0.828	-0.710	-0.783
Heavy drinking, average information	-0.522	-1.292	
Heavy drinking, information level 0	0.669*	-0.254*	0.511
Heavy drinking, information level 1	-0.067*	-0.851	0.194
Heavy drinking, information level 2	-0.804	-1.448	-0.908
Heavy drinking, information level 3	-1.540	-2.045	-1.653

Notes: Elasticity estimates marked by * are not statistically significantly different from zero. The weighted average price elasticities are calculated using weights based on the category shares accounted for by males and females.

for wine or distilled spirits. Price-induced substitution across beverage types appears to be very limited, but one study found significant cross-price substitution effects between distilled spirits and cigarettes. Finally, recent evidence suggests important differences in the price responsiveness of light, moderate, and heavy drinkers, with insignificant responses to price among many of the heaviest consumers of alcoholic beverages.

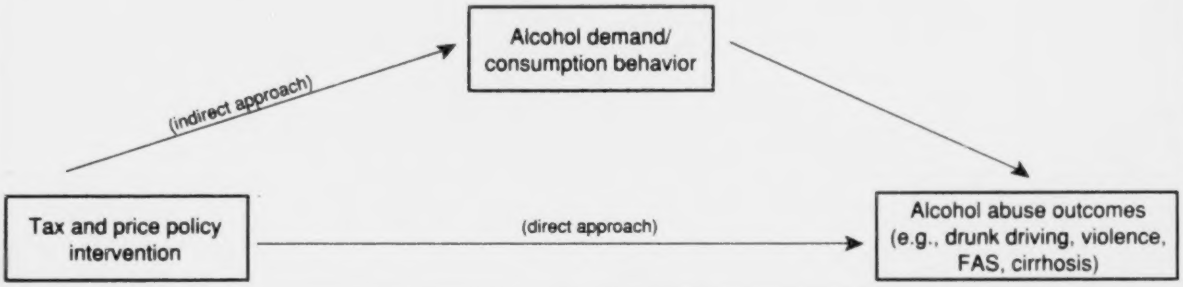
Analyses of Taxes or Prices and Alcohol-Related Problems

A number of studies have examined the relationship between alcohol prices or tax rates and adverse consequences associated with alcohol misuse. This literature builds on the seminal study by Cook and Tauchen (1982) that found a negative relationship between State excise tax rates on distilled spirits and cirrhosis mortality rates, which suggests that alcohol prices affect the consumption patterns of heavy drinkers. In another study that has become a landmark in this literature, Saffer and Grossman (1987) found that higher beer excise tax rates were associated with reductions in youth motor vehicle fatalities; both these studies used statistical methods similar to those employed in demand analyses. However, these studies examine the direct relationship between policy variables and alcohol-related health outcomes. This approach stands in contrast to traditional demand studies, which examine the effects of policy variables on alcohol consumption, with the subsequent connection to health-related outcomes often left unaddressed. Figure 2 depicts the difference between these two analytical approaches.

Recent research has extended the findings of these earlier studies. Chaloupka et al. (1993) used pooled time-series (annual, 1982–1988), cross-sectional (48 contiguous States) data to assess empirically how motor vehicle fatality rates are affected by various State alcohol control policies and driving while intoxicated (DWI) laws and State-level excise taxes on beer. In every specification, which included three definitions of the highway fatality rate (total fatalities, night driver fatalities, and alcohol-involved driver fatalities) and two alternative populations (all ages and 18- to 20-year-olds only), the beer tax rate exhibited large negative and statistically significant associations with fatalities. The magnitude of the estimated relationship was somewhat larger for the 18- to 20-year-olds than for all ages. Simulation analyses that estimated the hypothetical effect of increases in the beer tax rate found that increasing the Federal excise tax on beer in 1988 to match the Federal excise tax per unit of alcohol in distilled spirits would have reduced traffic fatalities by 5,771 in that year (approximately 12.8 percent), including a reduction of 1,822 fatalities among 18- to 20-year-olds (35.2 percent of traffic fatalities in this age group). Another simulation found that a policy to double the Federal excise tax on beer in 1988 (a policy that actually was implemented in January 1991) would have reduced traffic fatalities by 1,744 per year (3.9 percent) and by 611 among 18- to 20-year-olds (11.8 percent of traffic fatalities in this group).

A recent study (Ruhm 1995) that focused primarily on the relationships between macroeconomic conditions and alcohol-related problems estimated the relationships between beer taxes, minimum legal drinking age policies, alcohol use, and motor vehicle fatalities. This study employed a pooled time-series (annual, 1975–1988), cross-sectional (48 contiguous States) sample and controlled for unobserved State-level effects. Ruhm found

Figure 2. Empirical approaches to estimating effects of tax and price policies on outcomes relating to alcohol abuse.


Alcohol demand/ consumption behavior
(indirect approach)
Tax and price policy intervention
(direct approach)
Alcohol abuse outcomes (e.g., drunk driving, violence, FAS, cirrhosis)

statistically significant negative relationships between the State-level excise tax on beer and both total alcohol consumption and the State motor vehicle fatality rate.

Studies based on individual-level data have also suggested that higher alcoholic beverage prices and taxes may have significant negative relationships with the propensity to drive drunk. Kenkel (1993*b*) used data from the 1985 NHIS to assess the importance of alcoholic beverage prices and various alcohol control policies and drunk-driving deterrence measures as determinants of the number of occasions of drunk driving in the past year.

A two-stage modeling approach was used. In the first stage, the frequency of heavy drinking was modeled as a function of alcohol control policy variables (including prices), drunk-driving deterrence laws in force in the individual's home State, and other explanatory variables. In the second stage, the frequency of drunk driving was modeled as a function of the frequency of heavy drinking, drunk-driving deterrence laws, and other explanatory variables. Kenkel found that heavy drinking was a significant determinant of drunk driving for each subsample examined (males of all ages, females of all ages, males 21 and younger, females 21 and younger). Prices were significant determinants of heavy drinking for every subsample except for younger males. Kenkel estimated the elasticity of drunk driving with respect to the price of alcohol at -0.74 for males and -0.81 for females, which indicates that a given percentage increase in alcohol prices would yield a percentage reduction in occasions of drunk driving between three-fourths and four-fifths as large as the price change. This estimate is generally consistent in magnitude with the findings of earlier studies.

In every specification, the beer tax rate exhibited large negative and statistically significant associations with fatalities.

Mullahy and Sindelar (1994*b*) used data from the 1988 NHIS along with State-level data on beer taxes and various anti-drunk-driving policy measures to study factors that affect individuals' propensities to drive while drunk. The authors used regression analysis to generate separate estimates for males and females, with further subgroupings by race (white, nonwhite). They found that higher State beer tax rates were weakly associated with a reduction in propensity to drive drunk; the association was stronger for males than for females and for nonwhites than for whites (of either gender). There were somewhat more significant effects associated with various sociodemographic variables and with policies requiring mandatory license revocation and higher minimum fines for the first drunk-driving offense. The authors pointed out that the three policy measures considered together (beer taxes, license revocation, and minimum fines) had a highly significant association with the propensity for drunk driving.

Sloan et al. (1994) used State-level data for 1982–1988 to examine factors influencing mortality rates in six categories with some connection to alcohol abuse. The mortality categories were (1) alcohol as a primary cause, including chronic liver disease, alcoholic liver cirrhosis, and some other diseases; (2) traffic accidents; (3) homicides; (4) suicides; (5) several cancers to which alcohol contributes (cancers of the lip, oral cavity, pharynx, larynx, and liver); and (6) falls, fires, and all other accidents. Factors considered as explanatory variables included alcohol prices and various policy measures, such as laws requiring mandatory jail terms for first-time drunk drivers; dram shop laws assigning civil liability for damages caused by drinkers to licensed establishments where they have consumed alcohol; and policies not directly related to alcohol such as police services, gun control laws, mandatory seat belt laws, and no-fault auto insurance. Alcohol prices were found to have an insignificant effect on deaths attributed to diagnoses for which alcohol is a primary cause in all but one specification, which omitted variables reflecting State-specific effects. This result contrasts with the earlier findings of Cook (1981) and Cook and Tauchen (1982) of significant effects on cirrhosis mortality rates from taxes on distilled spirits. Perhaps more surprising, this study found only a marginally significant effect of alcohol prices on traffic crash mortality rates, even though most other published studies that have examined this relationship have found significant associations. The difference may be partly attributable to data differences: Sloan et al. (1994) used composite price data rather than the alcohol tax rates typically used by others (e.g., Chaloupka et al. 1993; Cook 1981; Saffer and Grossman 1987). Higher prices were related to significantly lower suicide rates and significantly lower mortality rates from cancers to which alcohol contributes. However, weak or insignificant effects of price were found for death rates from homicide and from falls, fires, and other accidents.

Finally, Cook and Moore (1993*b*) took a novel approach by considering alcohol tax policy as a potential tool for controlling violent crime. Using a time-series (annual, 1979–1988), cross-sectional (48 contiguous States) sample containing information on crime rates, alcohol consumption, excise taxes on beer, and other State-level characteristics, Cook and Moore found generally positive associations between alcohol use and crime rates (statistically significant for rape, assault, and robbery) and generally negative associations between real beer taxes and crime rates (statistically significant for rape and robbery).

Some studies by economists have found little or no evidence of any effect of alcohol advertising on consumption.

In sum, studies that have examined direct linkages between alcohol taxes or prices and various adverse outcomes that are often associated with alcohol consumption have found significant effects in many cases. These findings lend support to the view that tax or price policies can be useful tools to reduce alcohol-related harm. Nevertheless, further research is needed to clarify the full range of effects of these and other policy tools.

Economic Aspects of Alcohol Use and Alcohol Advertising

Conceptual and Methodological Issues

An issue of public health concern is the extent to which alcohol advertising affects the level of alcohol consumption and alcohol-related problems. Some studies by economists have found little or no evidence of any effect of alcohol advertising on consumption. These findings may be influenced by methodological issues that are especially relevant in this research area. Saffer (1993*b*, 1995) included comprehensive summaries of empirical research on the economic aspects of alcohol use and advertising; the following discussion follows the framework he established.

When assessing empirical work on the relationships between alcohol advertising and alcohol-related outcomes, the methodological implications of at least five key issues should be considered. First, to what extent are variations in advertising so small relative to the high overall level of advertising that they have little or no incremental impact on consumption? Second, what is the direction of causation between advertising and the outcome measure; that is, does differential alcohol advertising cause (in the statistical sense) differential alcohol consumption, does the level of alcohol consumption influence advertising decisions, or both? Third, what is the potential effect of alcohol advertising on alcohol prices (e.g., if advertising increases demand there may be increases in the price of alcohol, which in turn would dampen demand)? Fourth, how should advertising be measured? Finally, what outcome measure should be chosen (alcohol expenditure, alcohol consumption, measures of alcohol abuse, etc.)? Empirical investigations that try to account for any or all of these (or related) methodological considerations generally must employ special statistical methods or data bases or both that permit statistically unbiased assessment of the role of advertising on alcohol consumption behavior.

Saffer (in press) contends, for example, that the mixed pattern of results from many earlier studies of advertising and alcohol consumption (i.e., some studies identified statistically significant effects of advertising on consumption, others did not) is due partly to the fact that at high levels of advertising the "response function" becomes virtually flat so that there is very little incremental effect of additional advertising on overall consumption. Among the important earlier studies, Duffy (1987), McGuinness (1979), and Selvanathan (1989) found generally positive associations between alcohol advertising and consumption, but Bourgeois and Barnes (1979), Duffy (1991), Franke and Wilcox (1988), and Grabowski (1976) did not find statistically significant effects.

Findings that advertising has either no effect or only a small impact on alcohol consumption are consistent with the prediction from economic theory that advertising (like any other "input" in the production process) is subject to diminishing returns and, therefore, incremental changes in advertising beyond some level will have little or no effect on consumption behavior, at either the brand or the aggregate level. As a result, obtaining reliable estimates of the relationship between advertising and consumption may require data that exhibit substantial variation in the level of advertising, such as may be found in broad cross-sections, long time-series, and data that encompass timeframes in which there were advertising bans.

Recent Empirical Research

The most recent statistical analyses of the effects of alcohol advertising continue the pattern of inconsistent results established by earlier research. Generally, studies on the effect of aggregate advertising on alcohol consumption have not found a significant association. However, significant relationships between alcohol advertising and adverse health outcomes have been found.

Saffer (1991) analyzed the effects of alcohol advertising bans on various measures of alcohol consumption and alcohol abuse. The analysis was based on a pooled time-series, cross-sectional international data base composed of 17 developed countries over 14 years (1970 through 1983). The outcomes examined were per capita ethanol consumption, the liver cirrhosis mortality rate, and the motor vehicle fatality rate; various data adjustments were applied to obtain comparable measures of these variables across countries. Differential advertising ban policies across countries and over time served as natural experiments that provided the variation in the level of advertising needed to estimate relationships between alcohol advertising and outcomes related to alcohol consumption.

Saffer's results indicated that countries in which the advertising of spirits was banned had, on average, 84 percent as much alcohol consumption as countries with no bans once adjustments for other factors (e.g., price, income, drinking sentiment, and tourism) were taken into account. Countries in which beer and wine as well as spirits advertising was banned had consumption rates averaging about 89 percent of those countries in which only spirits ads were banned. Moreover, ad bans for spirits were estimated to result in motor vehicle fatality rates an average 10 percent lower than those in countries with no bans, and countries banning all beer, wine, and spirits advertising had fatality rates an average of 23 percent lower than countries banning spirits ads only.

Young (1993) questioned some of the findings in Saffer's study and presented contrasting results based on his reanalysis of a sample similar to that used by Saffer. In particular, Young's results support the hypothesis that there is some reverse causation running from alcohol consumption or abuse to advertising bans; they imply that intertemporal correlation of unobserved determinants of alcohol consumption and abuse resulted in some spurious statistical significance in Saffer's study; and they suggest that advertising bans actually were associated with increases in consumption levels when total alcohol consumption was disaggregated into its constituent components (beer, wine, and spirits). In response, Saffer (1993*a*), while claiming that extensions of the Saffer (1991) analysis might indeed be interesting, maintained that Young's results were themselves questionable and that it might be inappropriate to use them to guide policy decisions.

Lee and Tremblay (1992) estimated the U.S. market demand for beer to determine the effect of advertising on beer demand. They employed a time series of 31 annual observations of U.S. per capita beer consumption; price indexes for beer, whiskey, and soft drinks; and a measure of the quantity of beer advertising. In all statistical specifications reported, advertising exhibited a small positive influence on per capita demand, but the effect never approached statistical significance. The authors concluded that advertising probably influences firms' market shares but has no overall effect on the U.S. demand for beer.

Nelson and Moran (1995) used national time-series data for the United States in a more sophisticated modeling framework than that employed by Lee and Tremblay to arrive at the same basic conclusion: Alcohol advertising has little or no effect on aggregate alcohol consumption. In several specifications, the authors found that wine advertising had a weak but significant positive effect on wine consumption; that wine advertising had a very weak but significant negative effect on spirits consumption; and that spirits advertising had a weak but significant negative effect on wine consumption. All other beverage-specific effects were insignificant, including all effects involving beer advertising. In a final set of four models analyzing the demand for alcohol without regard to specific beverage type, alcohol advertising was insignificant, with negligible coefficient magnitudes in each case.

A recent study by Gius (1996) that examined the effects of distilled spirits advertising at the brand and industry levels concluded that brand-level spirits advertising results only in brand switching and does not increase the size of the spirits market. Using panel data for 1976–1989 on consumption, advertising, and price for 15 brands of distilled spirits (plus a residual "all other brands" category), Gius found that own-brand advertising was significantly associated with increased own-brand sales but that advertising by rival brands had only an insignificant effect on sales of a given brand.

A new study by Saffer (in press) used a pooled time-series, cross-sectional sample to examine the relationship between alcohol advertising messages and traffic crash fatalities. The unit of observation was the Area of Dominant Influence (ADI), which is a collection of counties within reach of a group of television transmitters. The data consisted of a total of 1,200 quarterly observations from 1986 to 1989 for the top 75 ADIs in the United States, which account for three-fourths of the U.S. population. This data set provided a high degree of cross-sectional variation relative to the data sources employed in many earlier studies.

Using regression models reflecting simultaneous determination of advertising levels and traffic fatality rates, Saffer found positive and statistically significant effects of alcohol advertising on motor vehicle fatality rates for most of the sample specifications analyzed. The estimated effects were stronger in analyses of fatality rates for all age groups than in analyses where the fatality rates were restricted to 18- to 20-year-olds. The estimated elasticity of traffic fatalities for all ages with respect to alcohol advertising messages ranged from 0.05 to 0.10. In addition, the estimated effect of alcohol prices on fatality rates was negative but insignificant in most specifications.

The regression results were used to predict the effects of two specific policy options: extension of the voluntary ban on broadcast advertising to include beer and wine and elimination of the tax deductibility of alcohol advertising expenses. After accounting for the likely effects of substitution to other media, Saffer concluded that a ban on broadcast advertising of beer and wine could reduce traffic deaths by 2,000 to 3,000 per year. He also estimated that eliminating the tax deductibility of alcohol advertising could reduce highway fatalities by about 1,300 per year, based on a 15-percent reduction in alcohol advertising expenditures. In addition, tax liability on the remaining advertising expenditures would raise tax revenues by about $300 million annually.

Alcohol Use and Labor Market Outcomes

Wages, Earnings, Income, and the Use and Abuse of Alcoholic Beverages

Conceptual and Methodological Issues

The hypothesis that excessive alcohol consumption has adverse consequences for employment and productivity has wide appeal, but causality is a key concern in examining the relationship between problem drinking and labor market outcomes. Excessive drinking as a cause of unemployment may be a plausible initial hypothesis, but drinking problems may be related to unobserved variables that also help to determine employment outcomes. In addition, there may be reverse causation (e.g., unemployment or occupational choice affects drinking behavior). These considerations of causality represent conceptual and statistical challenges to empirical studies in this area. The primary questions of interest concern the effects of alcohol use or problem drinking on various labor market outcomes: For example, does problem drinking (of some degree of severity) cause unemployment and, if so, what is the magnitude of this relationship? Does alcohol consumption at a particular level cause lower (or, perhaps, higher) wages and, if so, what is the magnitude of this relationship?

The main problem in attempting to give a causal interpretation to such relationships is statistical. There is no reason to expect that alcohol consumption or problem drinking behavior will be randomly distributed in the population. Instead, alcohol use or alcohol-related problems may be correlated with other factors unobserved by empirical analysis that help to determine productivity or labor market outcomes. As a result, statistical analyses may not be able to distinguish causal relationships ("treatment effects") from statistical associations that do not reflect direct causality.

One category of labor market outcomes of particular interest is measures of earnings or income. The focus on earnings stems, at least in part, from the theoretical relationship between earnings and productivity.[4] Analyses of the influence of alcohol consumption or alcohol problems must consider that earnings are the product of two distinct (yet related) economic quantities. The first is the wage rate; that is, the amount an individual receives for each unit of time worked (e.g., hourly wage). The second involves the amount of time the individual supplies to the labor market, if any. Earnings are the product of the wage rate and the amount of labor supplied

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[4] Standard economic theory holds that, in a competitive market with profit-maximizing firms and utility-maximizing workers, the wage a worker receives reflects the market value of the incremental production the worker provides. According to this theory, workers who are less productive (perhaps because of health problems) will earn lower wages, and observed differences in wages—other things being equal—may be interpreted as differences in productivity.

(e.g., a wage rate of $20/hour times 2,000 hours worked per year implies annual earnings of $40,000).

At the conceptual level, the important consideration is that alcohol use or problem drinking may have implications for the wage rate that differ from those for time worked. Because some empirical studies have focused on samples consisting only of working individuals (e.g., Berger and Leigh 1988; Cook 1991; French and Zarkin 1995), it is important to consider that the inferences drawn in those studies are conditional on the fact that individuals are already working. Some results (e.g., Kenkel and Ribar 1994; Mullahy and Sindelar 1993) suggest that there are important relationships as well between alcohol use or misuse and employment propensity and labor supply. To obtain an accurate view of the entire picture of such productivity relationships, each of these issues must be addressed.

> *When comparing the results of different studies, care should be exercised in making inferences about "alcohol and earnings," as the underlying measurements may be significantly different.*

Finally, it may be more difficult to discern the role of alcohol misuse in the labor market processes that determine individual income if income measures include components other than labor earnings, such as transfer payments (e.g., welfare payments and unemployment insurance) or the income of other household members. It would be absurd to argue, for example, that higher levels of transfer payments represent greater productivity, as eligibility for transfer payments often coincides with subpar productivity. To the extent that statistical analyses of factors affecting productivity rely on income data that include transfer payments received by the individual or household, they will produce biased estimates of the true effects. Similar arguments apply when analyzing household income measures; for example, alcohol problems could lead to increases in household incomes, other things being equal, if one spouse increases work effort to compensate for an anticipated alcohol-related reduction in the earnings of the other spouse.

Recent Empirical Research

Because of their theoretical linkages to worker productivity, the labor market outcomes most studied by economists interested in the economic consequences of alcohol consumption and alcohol abuse are wages, earnings, and income. Some studies have focused primarily on the effects of alcohol abuse or alcoholism; others have considered measures of alcohol consumption. When comparing the results of different studies, care should be exercised in making inferences about "alcohol and earnings," as the underlying measurements may be significantly different.

In one of the earliest attempts to relate alcohol problems in the household to economic success, Berry and Boland (1977) used data from the 1969 Berkeley Social Research Group Survey to relate household incomes to alcohol problems. For this study, alcohol problems were indicated by whether an alcohol-abusing male resided in the household (table 5). Berry and Boland found that households without an alcohol-abusing male had higher incomes (mean difference: 22.5 percent; median difference: 24.3 percent) than did households with alcohol-abusing males.

Benham and Benham (1982) used data on a sample of males who were children in St. Louis in the 1910s and 1920s and were either referred to a guidance clinic between 1924 and 1929 or selected as controls. To measure alcoholism, the authors used a binary variable indicating whether after age 18 the individual had a well-established addiction to alcohol without any other major psychiatric disorder (except neuroses). The effects of alcoholism on earnings were estimated to be negative but statistically insignificant.

In one of the best-known studies (commonly known as the RTI study) of the economic costs of alcohol-related problems, Harwood et al. (1984) used data from the 1979 National Survey of Attitudes and Interests in Drinking Practices and Problems ("National Alcohol Survey") to assess relationships between household income from all sources, alcohol consumption, and problem drinking as measured by a set of four indicators of alcohol-related problems. Results of the regression analyses indicated that problem drinking was associated with a 21-percent reduction in household income from all sources. The results also showed that after correcting for the adverse effects of problem drinking on income, consumption at levels up to about 2.5 ounces of alcohol per day was associated with increases in household income. Consumption at higher levels was associated with decreases in income.

Heien and Pittman (1989) criticized the validity of the RTI study on methodological grounds. Using the same data, they found in a raw comparison that households in which no problem drinker resided had incomes 13.6

percent *lower* than households that included at least one problem drinker. In a regression analysis, they found no statistically significant relationships between household incomes and either quantity/frequency measures of consumption or measures of problem drinking. Their critique suggests that the large difference in findings for similar analyses of the same data stems from a difference in regression methodology. A subsequent summary (Rice et al. 1990) of the issue rejected this explanation and questioned the validity of the Heien and Pittman results while implicitly acknowledging some of their other concerns. No published study has fully reconciled the sharply conflicting findings of these analyses.

The study by Rice et al. (1990), whose main objective was to update and revise the RTI economic cost estimates, contained new results on the relationship between alcohol abuse and income. The authors used multiple site data from the Epidemiologic Catchment Area (ECA) surveys in conjunction with the definition of ever meeting diagnostic criteria for alcohol abuse or dependence in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) (American Psychiatric Association 1987); the income measure was personal income. Their key finding was that lifetime alcohol dependence or alcohol abuse is negatively related to personal income for males and females, although the magnitude of the estimated relationship varies substantially by age and gender. Their results are summarized in table 6.

Berger and Leigh (1988) used data from the 1972–1973 Quality of Employment Survey (QES) to assess the relationships between alcohol consumption and wages. For this analysis, drinkers were defined as individuals who reported drinking alcoholic beverages at least one or two times per week. The key sample selection criteria were that the individual had to be at least 18 years old and working for pay at least 20 hours per week. Even with their most conservative approach to estimating wage differentials, the findings of Berger and Leigh suggest sizable wage advantages for drinkers over nondrinkers, with the differentials particularly large for females (21 percent, versus 8 percent for males). The results are summarized in table 7.

Table 5. Increase in annual income associated with having no alcohol-abusing male residing in the household—summary of key results from Berry and Boland 1977.

Age (years)	Mean % Increase	Median % Increase
21–29	23.1	24.4
30–39	21.0	22.0
40–49	23.8	26.4
50–59	11.6	14.5

Table 6. Reduction in annual personal income due to lifetime alcohol diagnosis, 1985—summary of key results from Rice et al. 1990.

Age (years)	Males		Females	
	%	$	%	$
18–24	1.4	131	0.8	75
25–34	3.0	807	2.8	484
35–54	5.5	1,958	11.9	2,141
55–64	9.3	2,295	18.7	1,900

Table 7. Percent that nondrinkers' wages are lower than drinkers' wages—summary of key results from Berger and Leigh 1988.

Calculation Method	Males	Females
I	12.8	25.5
II	7.8	20.9
III	36.2	28.7

In his survey of the social costs of drinking, Cook (1991) attempted to replicate the Berger-Leigh results using the QES sample described above; his results essentially confirmed the earlier findings. Although Cook's statistical analysis was more direct than the methodology used by Berger and Leigh, both studies reached essentially the same conclusion: At least over some range of moderate drinking, workers' earnings increase with alcohol consumption. Cook estimated a positive relationship between earnings and alcohol consumption of up to one drink per day. Unless concentrated on a few drinking occasions, this consumption level typically would not constitute problem drinking behavior. Cook found no statistically significant positive or negative association beyond this level of consumption; the results are summarized in table 8.

In a series of recent papers, Mullahy and Sindelar used data on males from the ECA survey's New Haven site to analyze a variety of relationships between alcoholism and

Table 8. Summary of key results from Cook 1991.

Alcohol Consumption	Median Annual 1972–1973 Earnings ($ thousands)
Never drinker	9.0
Less than one drink per year	8.5
Less than one drink per month	9.7
1–5 drinks per month	10.9
6–29 drinks per month	11.0
30–59 drinks per month	10.0
60–119 drinks per month	10.0
120 drinks per month and more	10.4

labor market success. The key results from this work pertaining to income were summarized in Mullahy and Sindelar (1993). In this study, the income measure was the individual's income from all sources. The authors considered several measures of alcohol problems, but their key results are based on the DSM-III-R measure of ever having met criteria for alcohol dependence or alcohol abuse or both. In raw comparisons (see table 9), individuals of all ages who had ever met criteria for alcohol abuse or dependence had significantly lower average incomes than those who had never met those criteria. However, the raw effect varied significantly by age group, with the most significant effect concentrated among those aged 45–59. In regression analyses focusing on the "prime working age" population (aged 30–59), Mullahy and Sindelar found that alcoholism has a negative and statistically significant relationship with individual income. The magnitude of the estimated relationship, however, depended crucially on what other covariates were controlled, with estimated income reductions due to alcoholism ranging from 17 to 31 percent.

Bryant et al. (1993) used data from the National Longitudinal Survey of Youth (NLSY) to study whether alcohol use affects labor market incomes; this analysis was confined to young white males. Several statistical models (in many respects analogous to those employed by Berger and Leigh) were used to obtain the result of primary interest: Wage rates and labor earnings of drinkers are greater than wage rates and labor earnings of nondrinkers (on the order of 25 cents per hour for the wage differential, on the order of $500 per year for the labor earnings differential).

Kenkel and Ribar (1994) also used data from the NLSY to characterize empirically a broad set of structural economic relationships involving alcohol consumption and young adults' socioeconomic success. This study presented a comprehensive set of estimates of the relationships between alcohol consumption and earnings and used a rich set of alternative statistical assumptions and methodologies as well as alternative definitions of drinking and problem drinking.

It is difficult to summarize the Kenkel-Ribar results simply; a general message is that problem drinking is often associated with reduced earnings for males and is sometimes associated with lower earnings for females. Some of the key estimates of earnings reductions due to problem drinking are summarized in table 10. In perhaps the most interesting and statistically sophisticated specifications estimated by Kenkel and Ribar, some of the magnitudes are considerable, on the order of 25 percent in some instances (in each case these correspond to the largest earnings reductions reported in the ranges in table 10). (Other results from the Kenkel and Ribar study are discussed later in this chapter.)

French and Zarkin (1995) collected data at four large work sites to address the question of whether moderate alcohol use is related to wages. Using regression methods designed to mitigate the problems of outlying observations in their sample, French and Zarkin analyzed the relationship between weekly wages and a set of drinking behavior measures. Their main finding was of an inverted U-shaped relationship between alcohol use and weekly wages; abstainers had lower wages than drinkers and heavy drinkers had lower wages than moderate drinkers. The peak of the alcohol-wage relationship estimated by French and Zarkin was in the range of 1.5 to 2.5 drinks per day.

Finally, Mullahy and Sindelar (1995) considered a related but distinct issue concerning wages, income, and welfare. In this study, the authors argued that many economic analyses of the determinants of productivity and their effects on economic welfare fail to account for uncertainty in wage and income outcomes. To the extent that individuals prefer to avoid risk and uncertainty and to the extent that drinking problems result in a more uncertain economic environment, using measured productivity differences to evaluate the welfare losses associated with alcohol problems will generally understate these welfare losses. Using the ECA sample described above, Mullahy and Sindelar provided empirical support for the hypothesis that problem drinking is associated with increases in the variance of income.

Table 9. Individual income (in thousands) by lifetime alcoholism status: raw comparisons (decrease or increase for alcoholic relative to nonalcoholic in braces)—summary of key results from Mullahy and Sindelar 1993.

	All Males			Full-Time Workers Only		
Age (years)	**Nonalcoholic**		**Alcoholic**	**Nonalcoholic**		**Alcoholic**
All Ages	20.8	{-16.3%}	17.4	23.2	{-10.8%}	20.7
Age Subgroups						
22–29	12.8	{+3.1%}	13.2	15.7	{-1.9%}	15.4
30–44	24.2	{-12.8%}	21.1	25.2	{+0.4%}	25.3
45–59	24.7	{-32.0%}	16.8	25.7	{-23.7%}	19.6
60–64	18.8	{+9.6%}	20.6	23.4	{+25.6%}	29.4

Table 10. Percentage reduction (increase if positive) in earnings due to problem drinking (range shown is across alternative statistical models)—summary of key results from Kenkel and Ribar 1994.

Problem Drinking Measure	Males	Females
Alcohol Dependence	-0.2 to -26.7	12.7 to -2.3
Alcohol Abuse	0.5 to -26.0	15.8 to -24.6
Heavy Drinking	0.4 to -11.1	0.3 to -10.3

In sum, recent studies have generally found significant adverse effects of alcohol abuse, alcohol dependence, or heavy drinking on earnings or income, at least for certain subpopulations. In contrast, a number of studies have found that, compared with both abstention and heavy drinking, alcohol consumption at moderate levels is associated with increases in earnings or income. One task that remains for future research is to elucidate the underlying labor market mechanisms that give rise to these associations.

Alcohol Use and Abuse, Labor Supply, and Employment

Conceptual and Methodological Issues

Economists typically distinguish three fundamental employment states. Individuals are either not in the labor force, in the labor force but not employed ("unemployed"), or in the labor force and working ("employed"). Labor supply is a general description of the number of hours individuals choose to work over any particular time interval. To understand the full effects of alcohol and alcohol-related problems on productivity, it is necessary to look beyond their effects on earnings to examine the implications of alcohol use behaviors for labor supply decisions.

Work loss or absenteeism may be considered one manifestation of labor supply behavior. The decision to miss work on what would otherwise be a scheduled work day is a decision not to supply labor to the market on that day. To the extent that drinking or drinking problems are found to be determinants of work loss, it is thus reasonable to interpret such relationships within this broader context of labor supply and employment issues.

Recent Empirical Research

Benham and Benham (1982) found in raw comparisons that alcoholics had an overall employment rate of 86 percent, while the rates for a sample of psychiatrically "well" individuals and a sample of nonalcoholics were 95 and 84 percent, respectively. For full-time employment, the rates were 79 percent for alcoholics, 90 percent for the well group, and 78 percent for nonalcoholics. In regression models that controlled for other components of human capital, the estimated relationships between alcoholism and employment (full- or part-time or military) were mixed: sometimes positive, sometimes negative, but in no instance even close to statistically significant.

Based on the New Haven ECA sample of males, Mullahy and Sindelar (1993) found that ever having met the DSM-III-R criteria for alcohol dependence or abuse was associated with a reduced probability of having worked for pay in each of the past 12 months (the authors termed this "full-time work"). Differences between those with and without alcohol problems were especially pronounced in analyses of specific age groups (see table 11). For males aged 30–44 and 45–59, the differences between the full-time work propensities of nonalcoholics and alcoholics were significant (88 vs. 73 percent in the younger group, 86 vs. 68 percent in the older group). Differences for younger (aged 22–29) and older (aged 60–64) workers were not statistically significant. However, significant negative effects of alcoholism did appear in a regression analysis of the determinants of full-time work that controlled for age, race, and other covariates.

Using the NLSY sample, Kenkel and Ribar (1994) employed a variety of estimation strategies to examine the number of hours worked by young adult males and females. In their benchmark models, Kenkel and Ribar found only small labor supply effects of heavy drinking, which were negative and statistically significant for males, positive and statistically insignificant for females. Alcohol abuse had small, positive, but statistically insignificant relationships with labor supply for both males and females. Using alternative statistical methods, however, Kenkel and Ribar found considerably larger and statistically significant positive effects of problem drinking on females' labor supply as well as considerably larger but statistically insignificant negative effects of problem drinking on hours worked by males.

Table 11. Full-time employment rates for males by lifetime alcoholism status—summary of key results from Mullahy and Sindelar 1993.

	Alcoholism Status	
Age (years)	**Nonalcoholic**	**Alcoholic**
All Ages	0.78	0.72
Age Subgroups		
22–29	0.65	0.74
30–44	0.88	0.73
45–59	0.86	0.68
60–64	0.57	0.57

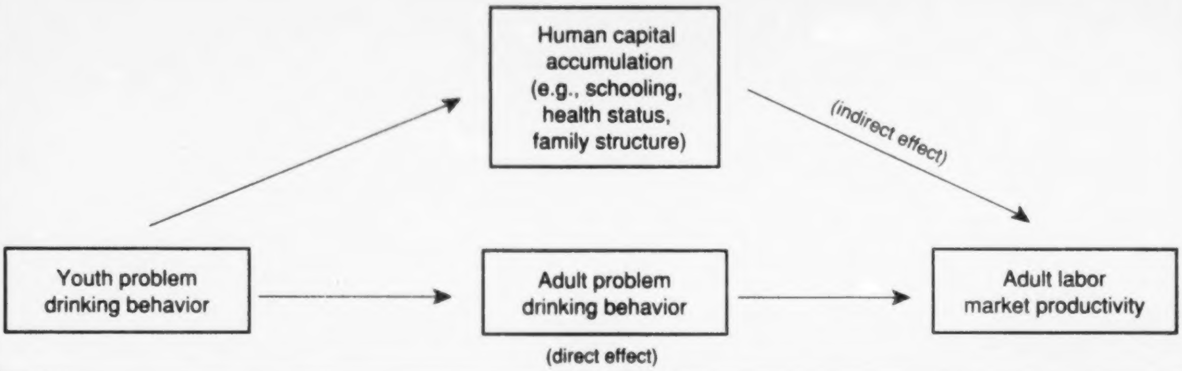
There has been little economic analysis of the relationships between work loss or absenteeism and alcohol use. An exception is the study by Manning et al. (1991), who used data from the Rand Health Insurance Experiment (HIE) and from the 1983 NHIS to test a set of hypotheses regarding work loss and alcohol use. Results from the analysis of the HIE data indicated that former drinkers had 38 percent more work loss than abstainers and infrequent current drinkers, but this finding was not supported by analysis of the NHIS data. For both data sets, these researchers found no statistically significant relationships for current drinkers between the monthly volume of reported alcohol consumption and the amount of work loss. Of course, these results are conditional in the sense that individuals can only lose time from work if they are already employed.

Alcohol Use and Human Capital

Mullahy and Sindelar (1989, 1993) have argued that standard analyses of the effects of drinking behaviors on labor market outcomes (e.g., earnings) may understate the true effects of the drinking behavior when the analyses include controls for other factors that also affect labor market outcomes. To the extent that other productive determinants (i.e., "human capital") of labor market outcomes are themselves affected by problem drinking, some of the effects of problem drinking on labor market outcomes are channeled through these other covariates. Economists usually identify the most important components of human capital as schooling attainment, work experience, health status, and family structure, but any factor that makes an individual's labor more productive or more highly valued in the market would be considered such a component. Mullahy and Sindelar contended that there may be indirect as well as direct effects of problem drinking on labor market success; for example, problem drinking might influence earnings both through a direct effect and indirectly by reducing education, effects on occupational choice, or influence on marital status. The indirect effects are mediated by the effects of problem drinking on human capital formation, which in turn affects labor market outcomes (figure 3).

Relatively little empirical research has examined how youth drinking affects either level of schooling attainment or educational performance. Results obtained by Mullahy and Sindelar (1989, 1994*a*) suggest that onset of alcoholism symptoms during youth is associated with

Figure 3. Direct and indirect effects of problem drinking on productivity.


Human capital accumulation (e.g., schooling, health status, family structure)
(indirect effect)
Youth problem drinking behavior
Adult problem drinking behavior
Adult labor market productivity
(direct effect)

reduced schooling attainment. They found that first onset of symptoms of alcoholism before age 19 was related to an 11-percent reduction in schooling attainment when other covariates were controlled; the raw difference was 8 percent. However, the direction of causality between alcoholism symptoms and schooling cannot be ascertained with confidence in this study.

Benham and Benham (1982) found that men meeting their definition of alcoholism (see page 290 had raw mean schooling attainments 24 and 15 percent below those of the "psychiatrically well" subsample and the nonalcoholic subsample, respectively. Given the considerable difference in the definition of alcoholism used in Mullahy-Sindelar and the Benham-Benham studies, the 11- and 15-percent differences in schooling attainment in the two studies are surprisingly similar.

Cook and Moore (1993*a*) used data from the NLSY to examine the relationship between youthful drinking behavior and educational outcomes. These authors related the highest year of schooling completed to a set of variables characterizing the individual's alcohol use and abuse behavior while in high school. They acknowledged the possibility of reverse causation (i.e., could the propensity for reduced schooling attainment result in alcohol abuse?) and employed statistical methods designed to circumvent this problem.

Cook and Moore's central finding was that several measures of high school drinking behavior (number of drinks per week, frequency of drinking, and frequency of being drunk) were negative and statistically significant determinants of the highest year of schooling completed. They estimated that frequent drinking while a high school senior resulted in completion of 2.3 fewer years of college than those completed by otherwise similar individuals who were not frequent drinkers.

Kenkel and Ribar (1994) examined how the probability of being married might be related to problem drinking for their NLSY sample of young adults. Across various statistical specifications and measures of problem drinking, Kenkel and Ribar estimated almost universally negative and statistically significant relationships between marriage probability and problem drinking for both males and females. This general result remained, although statistically somewhat weaker, when controls for possible reverse causation were included (i.e., marital status influencing drinking behavior rather than drinking behavior influencing marital status).

The message emerging from the empirical evidence available to date on this topic both within and outside economics (see, e.g., Miller-Tutzauer et al. 1991) is highly suggestive: Indirect effects of drinking and problem drinking may be as important as direct effects in determining labor market productivity. This message, in turn, suggests an important role for research in investigating the extent to which alcohol use and abuse (one's own or that of one's spouse, parents, or peers) might affect schooling attainment and educational performance, the formation of households, the level and quality of labor market experience, and other key components of human capital and the ultimate influence of these indirect effects on labor market productivity.

Summary

This chapter has presented an analytical overview of some of the themes and findings of recent research on economic aspects of alcohol use and alcohol abuse. Two main research areas have been highlighted. First, research continues to illuminate the role of economic factors as determinants of alcohol consumption and of various problems that often are associated with drinking. Using standard economic models of the determinants of consumption behavior, a substantial and growing body of research has established that consumption of beer, wine, and distilled spirits declines in response to increases in the prices or taxes associated with these beverages. Early results from a new area of emphasis in this research suggest that the relatively small group of drinkers with the highest consumption levels may be much less sensitive to price changes than are drinkers who consume at more moderate levels. A number of studies have also found that increases in alcoholic beverage taxes and prices are associated with reductions in motor vehicle fatalities and other adverse outcomes that are frequently associated with alcohol consumption. Finally, recent studies on the role of alcohol advertising as a determinant of alcohol consumption and alcohol-related problems continue the inconsistent pattern of results found in earlier studies. Several recent studies found no significant link between advertising and consumption levels, but another recent study found significant effects of advertising on traffic fatality rates.

The second major research area is the examination of the labor market consequences of alcohol consumption and various forms of problem drinking. Challenging conceptual and methodological issues confront researchers in testing hypotheses about the effects of alcohol problems on earnings, on labor supply decisions, and the interactions of past alcohol problems, past decisions affecting labor market outcomes, and current labor market behavior. Studies that have examined the relationship between alcohol consumption and earnings have found that both heavy drinkers and individuals who abstain from alcohol completely have lower earnings than individuals who drink at more moderate levels. However, studies have generally found pronounced negative effects of alcohol abuse and dependence on earnings and income levels. Research into the relationships between alcohol problems and individuals' decisions on whether and how much to work has yielded mixed results, with some findings varying especially by gender and age group. Finally, a relatively new area of research is finding support for hypotheses that alcohol problems may have indirect effects on earnings and employment by way of effects on educational achievement and marital status.

The past few years have seen enormous progress made, both conceptually and empirically, in specifying and estimating important policy-relevant economic relationships. Recent methodological advances (e.g., theories of advertising behavior and improved econometric techniques) have permitted and will continue to permit more ambitious empirical efforts in these areas of inquiry. When the availability of improved data sources that permit far more detailed investigations of these issues than have been possible to date is considered, one is left with considerable optimism about the prospects for meaningful economic analysis of behaviors associated with the use and abuse of alcohol and for greater applicability of the findings of this research to policies that can reduce the adverse consequences of alcohol abuse.

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Chapter 9

Prevention of Alcohol Problems

Introduction

The prevention of alcohol problems is an extremely broad and challenging issue. According to the public health model, prevention encompasses the individual (or host), the agent (alcohol in its many forms), and the environment in which an individual obtains or consumes alcohol (the immediate surroundings as well as the societal community). This model, which acknowledges the interplay among these three factors, has helped to expand the emphasis of prevention research efforts beyond alcohol problems in the drinker alone to include a recognition of the role that the environment plays in the onset and progression of alcohol abuse and alcoholism.

The research process begins with foundational studies from both the biomedical and the psychosocial sciences—which continue to provide insights about the genetic, psychological, and developmental factors that can heighten an individual's risk for alcohol disorders and related damage—and concludes with the actual testing of a single prevention strategy or multiple strategies in target populations. Additional steps in the research process include defining target groups in terms of problem prevalence, risk factors, and opportunities for interventions; identifying the most important objectives for a prevention strategy; and developing viable approaches that are aimed at the individual, the larger environment, or both. In the course of developing interventions, prevention researchers often must adapt or use existing measurement instruments or develop and test new techniques to assess the effectiveness of prevention programs. Findings from each of these phases enables prevention research to move forward in a logical and systematic fashion toward the primary goal of identifying ways to reduce the incidence of alcohol misuse and related problems.

This chapter highlights recent accomplishments in the prevention of alcohol-related problems and identifies themes needing further study. The information is presented from two perspectives: alcohol prevention approaches directed toward individual behavior and strategies designed to affect the environment in which drinking occurs.

The first part of the chapter presents studies of individual-level approaches, including school-based programs; family-based programs; college and university programs; programs for minorities, women, and other special populations; and community programs. The subsequent review of methodological issues in prevention research identifies factors that should be considered when interpreting findings from individual-level studies.

The second part of the chapter presents studies of environmental prevention approaches, including research on alcohol availability, alcohol warning efforts, prevention in the workplace, drinking and driving, violence prevention, and community-based prevention efforts. Although the chapter is divided into sections emphasizing the individual and the larger social environment, prevention efforts frequently integrate elements from more than one approach, and therefore similar issues may be considered in both sections. For example, the section on individual-level approaches touches on programs to prevent drinking and driving; these studies also involve environmental prevention components that are covered extensively in the section on environmental approaches.

Alcohol-related problems respect no age boundaries because alcohol is used by young people and adults of all ages. Adolescent drinking is widespread: Survey results indicate that most high school and junior high school students have at least experimented with alcohol (Johnston et al. 1996). Alcohol use by adolescents contributes significantly to alcohol-related problems in society because, once established, a pattern of alcohol misuse can be lifelong. Because of the broad implications of adolescent drinking, prevention efforts aimed at this population are of utmost importance and, accordingly, are emphasized in the chapter.

Individual-Level Approaches to Prevention

Throughout the 1970s and much of the 1980s, most approaches to the prevention of alcohol-related problems emphasized changing the attitudes, beliefs, skills, and behavior of *individuals*. These approaches are still common and likely will continue to be important in prevention practice. Individual-level approaches play a key role in the prevention efforts of many States and communities, and there is a sizable body of research on these programs.

Based on evidence and assumptions that attitudes, beliefs, and experiences contribute to a person's use of alcohol, individual-level prevention interventions deal with the characteristics of individuals and their proximal environments (e.g., family, peers, school, and workplace). Focusing on causal factors such as peer influence, family or workplace stress, and school failure, these interventions are designed to effect change in the variables within an individual that contribute to alcohol-using behavior.

The purpose of individual-level approaches is to remediate an individual's deficiencies, strengthen competencies, change beliefs or attitudes, or restructure proximal environments to reduce the risk for alcohol-related problems. Although, by definition, they target individuals, these prevention programs are often delivered in group settings, such as the classroom, the family, and the workplace. In fact, interventions that target individuals are rarely delivered individually. Thus, they also may have an impact on the characteristics of groups in which they are delivered. For example, a program based on hypotheses that family stress increases drinking and that financial difficulties increase family stress would teach family members coping skills or ways to manage money. At the same time, the program might alter group characteristics, such as the nature of social interaction patterns within the family.

School-Based Prevention Programs

Many individual-level approaches are school based. These programs are popular because they offer easy access to the target audience of young drinkers and potential drinkers. The main goals of school-based programs are to decrease the overall prevalence and level of drinking among youth; to reduce the progression of alcohol consumption to problem levels; and, ideally, to prevent a young person from starting to drink (Hansen 1993).

Although many school-based programs have been developed and implemented, experts debate their effectiveness (Hansen 1992; Moskowitz 1989*a*). Early programs emphasized scare tactics and provided information about alcohol, yet they showed little evidence of success (Schaps et al. 1981). Over time, however, programs improved as researchers applied increasing scientific rigor to program development. Recent programs are more sophisticated in their design, incorporating accepted social and psychological theories of behavior as well as findings from relevant studies that have helped to identify and define target audiences, determine the factors that trigger adolescent drinking, and devise strategies to prevent the onset of drinking (Hansen 1993).

Researchers also have begun to evaluate the effectiveness of specific program strategies; however, evaluating prevention programs in real-life settings presents a host of methodological challenges. For example, many programs suffer from selection bias and high attrition rates, both of which can influence study results. Furthermore, a program implemented in two different schools cannot be identical in content or format, even though the programs are based on the same theoretical model. Thus, different programs using the same approach often generate inconsistent evaluation results. Despite these methodological problems, recent alcohol prevention programs have offered some promising outcomes (Hansen 1992).

The following discussion reviews the design and effectiveness of recent school-based programs that focus on social influence and are based on three popular prevention strategies: life skills, resistance education, and normative education. Each of these strategies attempts to modify a particular factor (e.g., poor communication skills or peer pressure) that is believed to influence risk for drinking.

Life Skills

Life skills approaches are derived from a social learning model and emphasize the development of skills that enhance social interaction, interpersonal conflict resolution, and assertiveness (Botvin et al. 1984; Botvin and Wills 1990). One life skills program, the Life Skills Training (LST) curriculum (which focuses on increasing social skills and reducing interpersonal pressures to drink), has been evaluated with somewhat mixed results (Botvin et al. 1990*a,b*, 1992; Kreutter et al. 1991). Findings at 1-year followup for the program showed that peer-led LST reduced the frequency of both drinking and excessive drinking among the experimental group of junior high school students (grades 7 through 10), whereas teacher-led LST was effective with female students only (Botvin et al. 1990*a*). A 3-year followup study that examined effectiveness of teacher-led LST only, however, showed that the program had a positive influence on adolescents' frequency of getting drunk (Botvin et al. 1990*b*). In a 5-year followup study, the program's effects were maintained in 12th graders when the intervention protocol was delivered with high fidelity. Students' reports of alcohol consumption during the past week, of having more than three drinks on any recent occasion, and of drunkenness were all lower in program participants (Botvin et al. 1995).

> *The passage from elementary school to junior high is a critical time for adolescents because those who have begun to experiment with alcohol can start to misuse it.*

Resistance Education

Like life skills approaches, resistance education programs are rooted in social learning theory (McAlister et al. 1980). Resistance approaches, however, tend to focus exclusively on teaching young people to identify and resist situation-specific pressures to drink alcohol or use other drugs. Programs of this type build cognitive understanding as well as behavioral skills.

One of the earliest resistance training programs, Project SMART (Self-Management and Resistance Training), compared the effectiveness of a program emphasizing resistance skills with one based on affective education[1] to prevent the use of cigarettes, alcohol, and other drugs (Hansen et al. 1988). Hansen et al. reported that resistance training was effective in delaying drug use among seventh graders who participated in the program; affective education, however, was not successful. In addition, the program was more effective in preventing and reducing alcohol use among female students than among male students (Graham et al. 1990).

Project DARE (Drug Abuse Resistance Education) is a widely promoted resistance education program that is loosely modeled after Project SMART. DARE consists of 16 to 17 weekly 1-hour sessions conducted by uniformed officers and delivered primarily to fifth and sixth graders. The program includes both affective education (developing self-esteem and decisionmaking skills) and peer-resistance training (Ringwalt et al. 1991). Two well-controlled studies of DARE, one in Kentucky (Clayton et al. 1991) and one in North Carolina (Ringwalt et al. 1991), showed that DARE had little overall effect on alcohol use, although it affected such outcomes as self-assertiveness, attitudes about substances, perceptions about drawbacks associated with alcohol, and beliefs regarding peers' attitudes about drugs (Ringwalt et al. 1991). Clayton et al. (1991) suggested that the program may be more effective for students who score high on a measure of sensation seeking. Results from a recent meta-analysis of evaluations of DARE showed that the program has modest short-term (1-year) effects on reducing alcohol use (Ennett et al. 1994). Longitudinal data have revealed similar effects of the program (Ennett et al. 1994; McNeal and Hansen 1995).

Another resistance education program, the Alcohol Misuse Prevention Study (AMPS) (Dielman et al. 1989, 1992; Shope et al. 1992, 1993) consists of a four-session curriculum for fifth and sixth graders specifically designed to prevent alcohol use and misuse. The passage from elementary school to junior high is a critical time for adolescents because those who have begun to experiment with alcohol can start to misuse it. Accordingly, the program educates students about the short-term effects of alcohol use and misuse and offers extensive practice in developing peer-resistance skills.

The most striking results of the first phase of this program, AMPS 1, conducted between 1984 and 1988, occurred among high-risk sixth graders, defined as those who had some prior unsupervised alcohol experience at the time of the intervention. At 26-month followup, high-risk nonparticipating students increased their rate of alcohol misuse more than twice as much as high-risk trained students (Dielman et al. 1989, 1992; Shope et al. 1992, 1993, 1994). Similar findings were noted with respect to alcohol use. The effectiveness of the sixth-grade intervention among high-risk students persisted through grade 12 (Dielman 1995). Results also suggested that there is an optimal age for intervention: Researchers observed that intervention during grade 5 may be too early for an effective outcome (Dielman 1995). Upon additional followup, Shope et al. (1993, 1994) found less use and abuse of alcohol among students who had better refusal skills. Findings suggesting that the AMPS intervention was effective partly by reducing adolescents' vulnerability to peer pressure also helped to confirm the importance of peer influences on adolescent alcohol use.

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[1] Affective education emphasizes the development of personal capabilities, such as self-esteem, decisionmaking and problem-solving skills, and understanding how alcohol use can interfere with personal values and goals (Bangart-Drowns 1988; Tobler 1986).

AMPS 2, an expanded version of AMPS 1 that began in 1988, added parents and siblings to the original model. This revised intervention explores the influence of parental use or approval of alcohol, nurturance, permissiveness, sibling drinking, and self-image on a young person's decisionmaking and ability to use refusal skills to avoid alcohol misuse. The effectiveness of AMPS 2 is being tested.

In summary, recent, well-designed resistance education programs have produced somewhat positive, yet inconsistent, effects on alcohol use. Preliminary evidence suggests that these programs may have a differential positive impact on subgroups of students, such as high-sensation seekers (Clayton et al. 1991) or students who have experience with unsupervised alcohol use (Dielman et al. 1992). Confirmation of these effects awaits future research specifically designed to test them.

Normative Education

Young people consistently have been found to have erroneous normative beliefs; that is, they believe that alcohol use among their peers is more common than it actually is. Cross-sectional studies have shown that normative beliefs are potent predictors of alcohol use, heavy alcohol use, and alcohol-related problems (Klitzner et al. 1988; Vegega and Klitzner 1989). Building on these findings, Hansen and Graham (1991) conducted the Adolescent Prevention Trial, a program that compared the effectiveness of resistance training with normative education (a strategy that aims to correct erroneous beliefs about the prevalence and acceptability of alcohol use and to promote conservative attitudes about use that exists among peers). The investigators studied the effects of four curricula in the program: information only, information with resistance skills training, information with normative education, or information with resistance training and normative education.

At 1-year followup, alcohol use was significantly lower among students exposed to either curriculum with the normative education component (Hansen and Graham 1991; Hansen et al. 1991*a,b*). Students who did not receive normative education increased their alcohol use. Because resistance education alone had no effect, Hansen and Graham (1991) suggest that the past successes of programs using this prevention strategy could have occurred because many of them also had a normative component. Thus, changing normative beliefs appears to be an important and effective focus for school-based prevention efforts (Hansen 1993; Klitzner in press).

> *Young people consistently have been found to have erroneous normative beliefs; that is, they believe that alcohol use among their peers is more common than it actually is.*

Further evidence for the effectiveness of normative education in school-based programs is provided by the Midwestern Prevention Project, also known as Students Taught Awareness and Resistance (STAR) (Pentz et al. 1989). This comprehensive intervention comprises five components (school-based resistance training, parent education, mass media coverage of the program, community organization, and policy) that are introduced to junior high and high school students. Preliminary findings of the effects of the school program, which were analyzed through the 18-month followup, showed modest net declines in students' weekly prevalence rates of alcohol use (Pentz et al. 1989).

MacKinnon et al. (1991) noted that the students exposed to the program became less likely to believe in positive effects of alcohol use and were less likely to report that they would use alcohol in the future. Perhaps the most significant effect of the program was the students' changed perceptions of their friends' tolerance of alcohol use. The investigators suggest that the program achieved most of its effects by changing perceived peer-group norms about alcohol use.

Summary

As illustrated in the discussion above, early school-based programs were largely ineffective because of limitations in conceptualization, implementation, and evaluation. These pioneer programs, however, offered useful insight about improving the design and application of programs (Dielman 1995; Hansen 1992; Moskowitz 1989*b*). Recent studies in this area reflect the knowledge gained from early studies. Using enhanced methodologies and greater scientific rigor in design and implementation, more recent school-based programs have demonstrated greater effectiveness in reducing alcohol use and abuse in young people.

Family Programs

During the 1980s, alcohol prevention programs for parents and families increased substantially. This occurred, in part, because of growing evidence of the generational transmission of alcohol problems (Kumpfer and DeMarsh 1986) and because of preliminary findings suggesting that parental involvement in prevention programs may have a positive influence on parent-child communication about substance use. Parent and family programs range from providing simple alcohol and other drug education for parents to strengthening the family's role in the positive socialization of children.

> *Most college students (88 percent), including those under the legal drinking age, have used alcohol.*

The STAR intervention (described above) included a component for parents that combined home-based parent-child exercises, school-based parenting skills training, and communitywide activities to involve parents in prevention of substance use. Over an 18-month period, 72 percent of parents reported that they participated in one or more activities of the intervention, and 66 percent completed parent-child homework exercises (Rohrbach et al. 1995). Only 25 percent, however, participated in parenting skills training. Results suggested that parent participation in the program could be effective in reducing adolescent substance use, although the effect was greater for cigarette use than for alcohol use. Furthermore, parental participation seemingly influenced young people's selection of non-drug-using friends. Parental participation, parental substance use, and the degree to which adolescents cared about their parents' expectations were significantly associated with adolescent substance use, thus providing support for the importance of involving parents in drug abuse prevention programs.

College and University Programs

Most college students (88 percent), including those under the legal drinking age, have used alcohol (Johnston et al. 1996). Developmentally, the ages 18 through 21 years is the period of heaviest alcohol consumption for most drinkers in the United States (Chen and Kandel 1995). Thus, alcohol consumption and related problems are of considerable concern to colleges and universities (U.S. Department of Education 1994). Results of the Monitoring the Future Study (Johnston et al. 1996) suggest that drinking by college students is similar to drinking by young adults who are not in college, with one very important exception: The rates of heavy or "binge" drinking—consuming five or more drinks on a single occasion or "drinking to get drunk"—are considerably higher among college students than among young adults not in college. This difference, which is especially pronounced among women, has increased over the last decade. Among college women, the rates of binge drinking have remained relatively steady since 1980, whereas rates among their noncollege counterparts have steadily decreased.

In a longitudinal study of college drinking, Wechsler et al. (1994) characterized binge drinking as a pattern that begins in high school and persists through the college years. The researchers suggested that because risky drinking in college appears to be a continuation of use patterns established in high school, individual-level drinking programs for college students may need to focus on early detection and intervention rather than primary prevention.

A prevention program directed toward college students is the High Risk Drinkers Project at the University of Washington (Marlatt et al. 1993). Freshmen participants are selected by their reports of risky drinking or alcohol-related problems before entering the university. The program is based on a "stepped care" model, in which increasingly intensive interventions are offered according to individual participants' needs. The first step is a 1-hour motivational intervention; later steps include increasingly more intensive counseling. Marlatt et al.

(1993) reported that program participants had significantly lower levels of both drinking and alcohol-related problems than a randomly assigned control group over a 2-year followup period.

An improved research design, a larger sample, and a longer followup (4 years) characterize the University of Washington's Lifestyles '94 Project, a replication and expansion of earlier studies targeting students who are heavy drinkers (Marlatt et al. 1995). The investigation, which focuses on harm reduction for younger students (specifically, freshmen aged 19 years or younger at the beginning of the study), is expected to contribute to the knowledge base about individual differences in response to interventions.

Programs for Minorities, Women, and Other Special Populations

The drinking patterns, alcohol-related problems, and prevention needs of minorities, women, and other special populations (e.g., disabled persons) are generally believed to differ from those of the white, male population in which most individual-level prevention strategies have been tested. Researchers have made progress in defining these differences for African Americans (Brown 1993; Clifford and Jones 1988), Native Americans (Fleming 1992; James et al. 1993; Young 1993), Hispanics (Goldberg and Botvin 1993), and persons with disabilities (Elmquist et al. 1992). With this progress, however, has come new questions to be answered. For example, although prevention efforts that are effective within the general population also appear to be useful for some minority groups (Gilchrist et al. 1987), it is unclear whether minority populations would benefit from interventions specifically designed for them.

Some evidence suggests that women may benefit from specialized prevention approaches.

Some evidence suggests that women may benefit from specialized prevention approaches (see, for example, Nirenberg and Gomberg 1993). For example, epidemiologic data indicate that the antecedents, onset, drinking behaviors, and drinking consequences can differ between men and women (see Chapter 1, Epidemiology of Alcohol Use and Alcohol-Related Consequences). In addition, a growing body of research suggests that women may be at higher risk for developing alcohol-related problems at lower levels of consumption than men. Men and women also appear to display different manifestations of alcohol abuse as well as dissimilar social and health consequences from their drinking (Lex 1990) (see Chapter 5, Effects of Alcohol on Health and Body Systems). These differences suggest that gender-specific prevention approaches may be particularly effective for women, although more research will be necessary to critically evaluate and compare outcomes for men and women exposed to similar interventions in gender-specific environments.

Several recent studies have concentrated on high-risk populations, including ethnic minorities and special needs individuals. One program used peer counseling, the development of coping skills, and alcohol education in a population of Native American adolescents (Gilchrist et al. 1987) and found that young people who were exposed to the intervention drank less than control individuals 6 months after completing the program. In another study, a 5-day summer camp experience for Native American youth resulted in short-term decreases in substance use at 30-day followup (Conner and Conner 1993). The campers also more often expressed their intention not to drive while impaired. Finally, a primary prevention program for children of kindergarten age and their mothers in a Chicago housing project showed some positive trends (e.g., mothers returning to school and seeking substance abuse treatment), although the program did not significantly affect alcohol use (Ruch-Ross 1992).

The alcohol research field is addressing the alcohol prevention needs of minorities and other special populations. Evaluating existing data is the first step in developing rigorous, controlled studies of new techniques designed to meet the special needs of minority persons who may be at risk for alcohol-related problems. Such prevention strategies may draw on the results of both individual- and environmental-level prevention research in meeting the specific needs of individuals and the communities in which they live.

Community Programs

Communitywide and community-based substance abuse prevention programs are rapidly becoming among the most popular responses to alcohol and other drug problems in the United States (Giesbrecht et al. 1993; Klitzner et al. 1993). In addition to numerous environmental factors (Giesbrecht et al. 1993; Hingson in press), community programs often incorporate strategies directed toward individuals.

Individual-level strategies can support environmental strategies. For example, lowering the legal blood alcohol concentration (BAC) limit for teen drivers (an environmental strategy) in Maine, New Mexico, North Carolina, and Wisconsin significantly reduced nighttime fatal crashes by teenage drivers (Hingson et al. 1991). Surveys in Maine, however, revealed that many young people did not know about the law or the consequences of violating it. An information campaign targeting adolescents (an individual strategy) increased the law's effectiveness in reducing crashes (Hingson 1992). Together, environmental (legislation and enforcement) and individual-level (information) strategies had a maximal effect on this alcohol-related problem.

Reaching youth in community settings after school is an appealing individual-level strategy because young people often bond more with coaches and activity leaders than with teachers. Community program staff, many of whom have natural talent for dealing with youth in a nonauthoritarian manner, have the potential to understand and deal with the personal issues facing adolescents. A program designed for Boys & Girls Clubs called Stay SMART has recently shon promise as an individual-level alcohol prevention strategy implemented in a community setting (St. Pierre et al. 1992). The program is designed to teach participants multiple social and personal competence skills as well as to help them to identify and resist various pressures to use alcohol and other drugs. Researchers found that the program alone, and also in conjunction with booster sessions, had some effect on alcohol-related behaviors (frequency and amount of alcohol use). However, only the combination of program and booster sessions helped to diminish over time adolescents' perceptions of the social benefits of drinking.

Project Northland, an ongoing communitywide prevention program in 24 school districts in Minnesota, implements both individual and environmental prevention approaches simultaneously and consistently in all participating communities (Wagenaar and Perry 1994). The program emphasizes prevention of alcohol use among 10- to 14-year-olds. Individual level approaches within the program recently have yielded some promising results.

Program interventions are applied during the sixth, seventh, and eighth grades. Sixth-grade students take part in the "Slick Tracy Home Team Program," a home-based program (named for the program's theme-oriented "Slick Tracy" comic narrative) aimed at parents and children (Williams et al. 1995). Seventh-grade students participate in the "Amazing Alternatives!" intervention, which provides participants and their parents with ways to resist and counteract influences that encourage teens to use alcohol. Eighth-grade students participate in the "PowerLines" intervention, which introduces them to the "power" groups in their communities that influence adolescent alcohol use and alcohol availability and also teaches them about community action and citizen participation skills.

Williams et al. (1995) reported that participation in Project Northland was high within all three grades, even among students who researchers thought would have reduced participation due to their risk status. Approximately 90 percent of parents also became involved in the program's alcohol education activities. Results from the study showed that the interventions successfully reduced adolescent alcohol use, the tendency to use alcohol, and the combination of cigarette and alcohol use among program participants. The interventions were more effective among students who had not yet used alcohol at the beginning of the sixth grade (Perry et al. in press). The program also had positive effects on peer pressure to use alcohol and introduced skills to adolescents to help them resist peer pressure. Finally, Project Northland helped to improve communications between parents and children about the consequences of drinking.

Methodological Issues in Prevention Studies

Unique methodological problems complicate prevention studies, which affect the evaluation of all prevention efforts. Most evaluations involve quasi-experimental designs to compare groups of individuals who participated in programs with those who did not. The strength of such evaluations often is the inclusion of data that can help to eliminate plausible rival hypotheses—data that natural experiments (common to environmental approaches) often lack. Reviews of prevention research (e.g., Bruvold and Rundall 1988; Hansen 1992; Moskowitz 1989*b*) suggest that methodological problems have not always been adequately addressed in studies, thereby compromising the conclusions sometimes. However, there also is more recent evidence that research has consistently advanced the methods used to evaluate preventive approaches (Dielman 1995).

Among common methodological problems in prevention studies are statistical analyses, measurement procedures, comparability of groups, and attrition rates

(Moskowitz 1989*a*). Several of these problems are reviewed herein.

The statistical methods used to analyze most individual-level prevention studies require that the same units be assigned to experimental conditions as are used in the analyses. An experiment to measure an individual subject's alcohol use should be designed so that each subject is a separate unit in the analysis; randomization should ensure that each subject has an equal likelihood of being assigned to each experimental condition. In studies of school-based prevention, classrooms or even schools may be assigned to conditions, but the analyses involve data from individuals. Analyses of variance (or ANOVA), covariance (or ANCOVA), and multiple regression analyses of such studies yield biased estimates of program effects and inflated probability estimates (Moskowitz 1989*b*). Methods of correcting for these effects have recently been adopted (Murray and Hannan 1990; Murray and Wolfinger 1994).

Individual-level prevention program studies often rely on self-reports to measure alcohol use and related problems. When such reports pertain to socially sensitive behaviors, such as drinking, they are subject to biases that may result in underreporting of alcohol use or problems (Moskowitz 1989*a*). Conversely, self-report biases are consistent over time, thus allowing unbiased estimates of trend data (Johnston et al. 1992).

Differential biases in self-reports may exist between program and comparison groups. For example, students exposed to heavy doses of moral persuasion intervention may be more reluctant to report driving after drinking. Methods to enhance the validity of self-reports, such as "bogus pipelines" (an attempt to increase the veracity of self-reports by telling subjects that their responses will be checked against corroborating tests, such as saliva or urine samples) (Evans et al. 1977) or biological assays, may introduce additional biases, thereby reducing the overall validity of the studies (Moskowitz 1989*b*). However, a study of the effects of a saliva pipeline procedure on the validity of alcohol use reporting among sixth graders revealed small and inconsistent effects (Wagenaar et al. 1993*a*).

Issues of self-report validity are closely related to the unit of analysis problem. The assignment of larger units of analysis, such as schools and communities, to experimental conditions increases the possibility of using archival records to supplement self-reports (Klitzner et al. 1993). When the individual is the unit of analysis, however, self-report is often the only feasible method of collecting data on alcohol use and related problems.

Although they are potent determinants of alcohol use and related problems, environmental variables are not addressed in most individual-level prevention programs. Ideally, such variables would be controlled in individual-level prevention outcome studies; however, it is often impossible to control for them.

Because manipulation of environmental variables (e.g., media campaigns and changes in alcohol taxation) usually occurs at the State or national level, such changes have the potential to affect equally all participants in a prevention study. More localized changes in environmental variables (e.g., school alcohol policy and alcoholic beverage control regulations), however, may affect only a portion of individual-level prevention study participants. For example, in a multicommunity evaluation of Students Against Driving Drunk, a local media campaign and police crackdown on youth drinking hindered the opportunity to conduct cross-community comparisons (Klitzner et al. 1994).

Environmental changes may mask the effects of individual-level interventions, which are usually more difficult to discern. The extent to which such dilution affects prevention studies is unknown but constitutes a potential problem in interpreting the results of studies in progress at the time of major alcohol policy changes (e.g., increased legal minimum age for purchase of alcohol).

In summary, methodological considerations dictate caution in interpreting the results of all prevention studies, in particular individual-level prevention studies. Recent research has been designed to address these issues, and the validity of individual-level prevention studies has been improving steadily.

Environmental Approaches to Prevention

Prevention efforts that focus on the entire population of drinkers, not only a small "high-risk" segment, represent an important element in the prevention of alcohol problems (Syme 1986), for several reasons. First, it is impossible to identify in advance all individuals who are at high risk for alcohol problems and thus need special interventions. Because more than one-half of the entire population drinks (see chapter 1) and many drinkers experience moderate to severe alcohol-induced impairment at least occasionally, a large segment of the population may be at significant risk for a car crash, assault, rape, injury, or other health problem associated with their drinking. Second, the magnitude of alcohol-related problems is such that even if there were a perfect cure for all persons at high risk, resources likely would be insufficient to apply this cure to all who need it. Third, there is constant turnover in the high-risk segment of the population. New members are constantly entering the pool of those at high risk, while others leave the high-risk pool.

Finally, most alcohol-related deaths and disabilities are attributable to moderate drinkers, not to those addicted to alcohol (Kreitman 1986). The heaviest drinkers clearly are at highest individual risk for problems. Because so many more people are in the lower risk, "moderate" drinking group, however, a lower individual risk still results in a larger aggregate burden to society. This is the classic "population-attributable risk" concept in epidemiology (Lilienfeld and Lilienfeld 1980) that often is overlooked in designing programs focusing solely on high-risk drinkers.

> *When attention turns to ways to best minimize alcohol problems across the population, however, prevention efforts must address the conditions that give rise to risky drinking practices.*

Alcohol use is a social behavior heavily influenced by the social structures, norms, and other dimensions of the environment in which people live (Akers 1992). Drinking patterns in the majority of the general population reflect these influences. Determining why a given individual will drink and understanding the consequences of individual drinking is important in a clinical setting, where a small set of individuals with alcohol-related problems are the focus of attention. When attention turns to ways to best minimize alcohol problems across the population, however, prevention efforts must address the conditions that give rise to risky drinking practices. Figure 1, on the next page, represents the integration of numerous theories that address drinking behavior, from individual-level factors to societal factors (Wagenaar and Perry 1994).

Although many dimensions of the social and policy environment may affect drinking and associated health problems, only a few have been evaluated scientifically. Recent research has focused on studies of alcohol distribution systems, server behavior, minimum drinking age, warning labels, and workplace policies. In addition, some studies have examined policies related to legal liability and hours or days of sale.

Alcohol Availability Issues

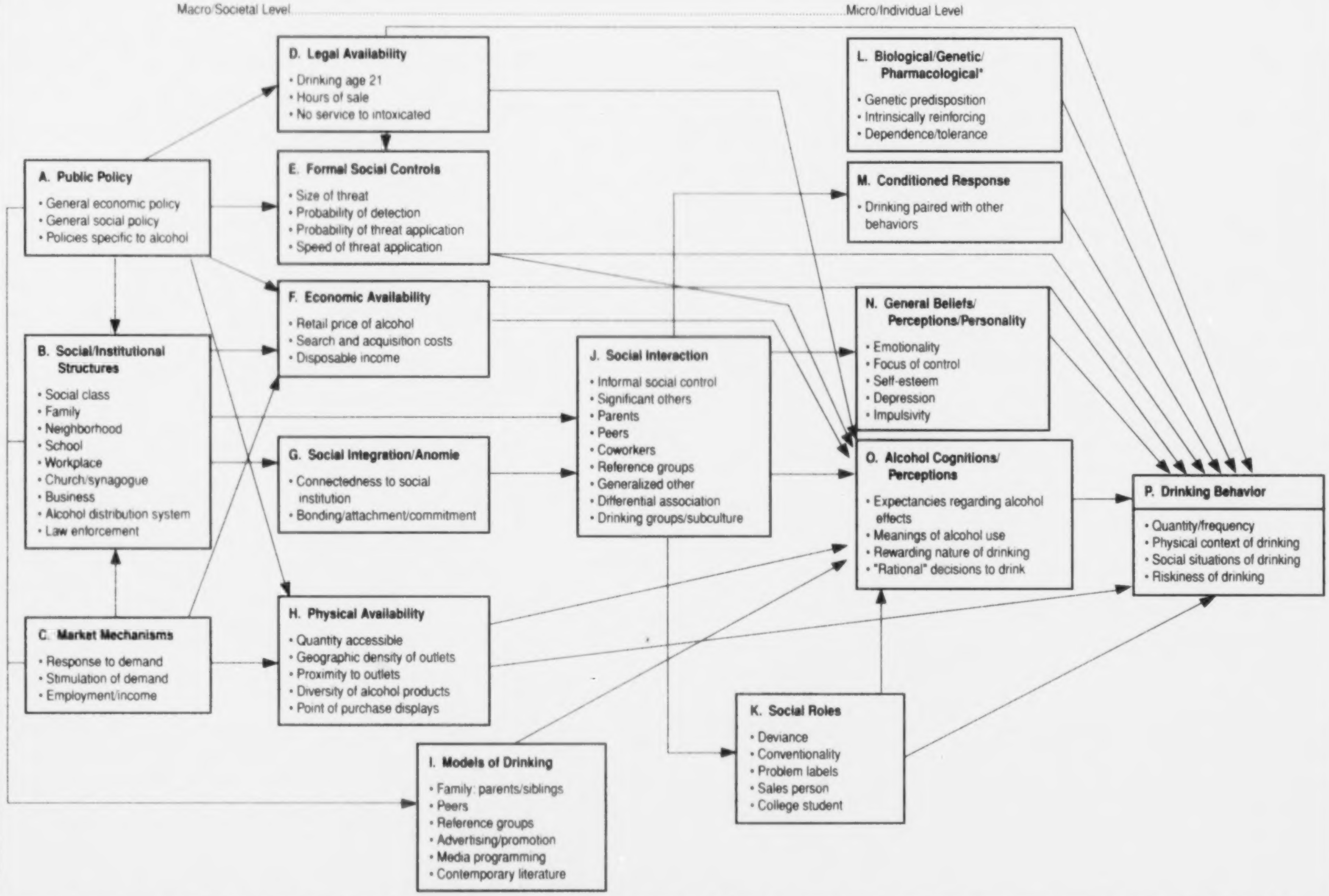
In research, alcohol availability commonly is defined along physical, social, legal, and economic dimensions (Gruenewald et al. 1993). *Physical availability* refers to the extent to which alcohol purchase is convenient and often is measured in terms of alcohol outlets in consumers' physical environments. *Social availability* refers to the prevalence of alcohol use in consumers' social environments, usually measured according to self-reports of the amount of alcohol served at social occasions. *Legal availability* refers to the effect of laws, regulations, and policies (such as minimum drinking age laws and alcohol distribution systems) on levels of alcohol consumption and consequent problems. *Economic availability* refers to the effect of the price of alcoholic beverages and consumers' income on the amount of alcohol consumed (see Chapter 8, Economic Aspects of Alcohol Use and Alcohol-Related Problems, for a discussion of economic availability research).

This framework is a useful way to examine and categorize availability issues. However, many studies in this area do not easily fit within one dimension of availability but rather consider the relationship among multiple dimensions of availability, consumption levels, and alcohol-related problems.

Alcohol Distribution Systems

Physical and legal availability to alcohol can be modified through public policies that affect access by regulating alcoholic beverage distribution systems. These systems vary from State to State along a continuum that ranges from State monopolies to privatized license systems. For example, a State may have a monopoly system for one type of alcoholic beverage (e.g., distilled spirits) and a license system for others (e.g., wine and beer) at either the wholesale or the retail level or both (Wagenaar and Farrell 1989). The commonly held view of a simple dichotomy between monopoly and license systems is inadequate to characterize differences in the extent of control on alcohol distribution across States (Janes and Gruenewald 1991).

Figure 1. An integrated theory of drinking behavior.


Macro/Societal Level
Micro/Individual Level
A. Public Policy
• General economic policy
• General social policy
• Policies specific to alcohol
B. Social/Institutional Structures
• Social class
• Family
• Neighborhood
• School
• Workplace
• Church/synagogue
• Business
• Alcohol distribution system
• Law enforcement
C. Market Mechanisms
• Response to demand
• Stimulation of demand
• Employment/income
D. Legal Availability
• Drinking age 21
• Hours of sale
• No service to intoxicated
E. Formal Social Controls
• Size of threat
• Probability of detection
• Probability of threat application
• Speed of threat application
F. Economic Availability
• Retail price of alcohol
• Search and acquisition costs
• Disposable income
G. Social Integration/Anomie
• Connectedness to social institution
• Bonding/attachment/commitment
H. Physical Availability
• Quantity accessible
• Geographic density of outlets
• Proximity to outlets
• Diversity of alcohol products
• Point of purchase displays
I. Models of Drinking
• Family: parents/siblings
• Peers
• Reference groups
• Advertising/promotion
• Media programming
• Contemporary literature
J. Social Interaction
• Informal social control
• Significant others
• Parents
• Peers
• Coworkers
• Reference groups
• Generalized other
• Differential association
• Drinking groups/subculture
K. Social Roles
• Deviance
• Conventionality
• Problem labels
• Sales person
• College student
L. Biological/Genetic/ Pharmacological*
• Genetic predisposition
• Intrinsically reinforcing
• Dependence/tolerance
M. Conditioned Response
• Drinking paired with other behaviors
N. General Beliefs/ Perceptions/Personality
• Emotionality
• Focus of control
• Self-esteem
• Depression
• Impulsivity
O. Alcohol Cognitions/ Perceptions
• Expectancies regarding alcohol effects
• Meanings of alcohol use
• Rewarding nature of drinking
• "Rational" decisions to drink
P. Drinking Behavior
• Quantity/frequency
• Physical context of drinking
• Social situations of drinking
• Riskiness of drinking

*Biological, genetic, and pharmacological factors, which have been compressed into one box for the purposes of this figure, are diverse, multiple variables that contribute to drinking behavior. These variables are the focus of a large body or research in the alcohol field.

Source: Wagenaar and Perry 1995. From *Alcohol Problems Among Adolescents: Current Directions in Prevention Research* (p.000), by G.M. Boyd, J. Howard, and R.A. Zucker, editors, 1995, Hillsdale, NJ: Lawrence Erlbaum Associates 1995. Reprinted by permission.

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During the 1970s and 1980s, several States implemented significant changes in their alcohol distribution systems. Policy changes increased alcohol availability by permitting the sales of a particular type of beverage (e.g., wine or distilled spirits) in licensed private outlets rather than limiting sales to State-owned and -operated liquor stores. In some States, the number of alcohol outlets increased substantially with privatization; marketing and promotion of alcoholic beverages at the retail level also increased.

Early in the 1990s, several studies examined the effects of such policy changes on sales and the consumption of alcoholic beverages. Wagenaar and Holder (1991*a*) performed a time-series evaluation of the effects of a 1985 policy change privatizing wine sales in Iowa and a similar 1981 policy change in West Virginia. Their results showed that after controlling for national trends and other factors, wine sales increased by 93 percent in Iowa and by 48 percent in West Virginia. Similarly, privatizing distilled spirits sales in Iowa led to a 10-percent increase in sales (Holder and Wagenaar 1990).

Results from several studies have shown that the elimination of State alcohol retail monopolies and the introduction of licensed private sales outlets substantially increase alcoholic beverage sales and consumption.

Fitzgerald and Mulford (1992) evaluated the effects of privatization of retail wine and distilled spirits sales in Iowa by using survey data on drinking among persons aged 18 and older before and after the policy changes. The investigators found no significant increases in self-reported consumption up to 46 months after wine sales privatization and 25 months after spirits sales privatization. Time-series analyses of Iowa wine sales data from 1980 to 1990 (Mulford et al. 1992) showed temporary wine sale increases that dissipated over time. In a subsequent commentary, however, Wagenaar and Holder (1993) suggested that failure by Mulford et al. (1992) to control for national trends in alcohol sales during the period evaluated may have affected their findings. In a recent replication of time-series evaluations of policies on wine sales privatization in five additional States, Wagenaar and Holder (1995) demonstrated increased wine sales of 15 percent in New Hampshire, 42 percent in Alabama, 75 percent in Montana, 137 percent in Maine, and 150 percent in Idaho.

Thus, results from several studies have shown that the elimination of State alcohol retail monopolies and the introduction of licensed private sales outlets substantially increase alcoholic beverage sales and consumption. Privatization of distribution systems typically results in several concurrent changes in alcohol availability, including increases in the number of sales outlets, longer sale hours, and permitted use of credit cards as well as increased price promotions and advertising (Wagenaar and Holder 1991*a*). However, it is difficult to disentangle and evaluate the role of these various components of a privatization policy.

Density of Alcohol Outlets

The density of alcohol outlets in a given area or community also can influence physical availability to alcohol and hence may affect alcohol consumption and potential problems that can occur with increased drinking. Van Oers and Garretsen (1993) explored the relationship among outlet density, alcohol use, and traffic crashes by using 3 years (1987–1989) of consumption data for randomly selected Rotterdam residents as well as data on traffic injuries and bar and liquor store densities within the city. The researchers found a significant positive relationship between the rate of traffic injury and the density of bars and liquor shops, suggesting that high outlet densities are a significant risk factor for traffic injuries at the neighborhood level. In addition, neighborhoods with higher densities of liquor shops had a significantly higher percentage of drinkers. A similar relationship between density of bars and percentage of drinkers was not observed.

Although such results suggest that the density of liquor stores influences levels of drinking, the actual association is not so clear. Liquor store density may result from the high percentage of drinkers in a particular area, with entrepreneurs locating their liquor stores where they perceive a good market for alcohol. If so, the observed relationships between outlet density and alcohol problems, such as traffic crashes, may, in fact, be due to a previously higher percentage of drinkers in those areas.

Gruenewald et al. (1993) explored this issue of which came first—higher outlet densities or higher drinking rates. Using U.S. data for 1969 to 1987 with two-stage least-squares regression modeling, the investigators explored the reciprocity in the relationship between alcohol sales and numbers of outlets (i.e., higher sales may cause more outlets and more outlets may result in higher sales). Controlling for such variables as income and price effects, minimum drinking age, tourism, land area per adult, and religious preference, these researchers found a direct positive relationship between density of alcohol outlets and wine and spirits sales; they did not assess the relationship with beer sales. The reverse relationship (i.e., effect of alcohol sales on density of outlets) was not statistically significant. The results of this study, along with the results of privatization policy studies—which typically show that outlet density increases with privatization—suggest that increased outlet densities are associated with increased alcohol sales.

> *A recent review of more than 50 studies conducted in the 1980s provided evidence that raising the legal drinking age to 21 effectively reduced youth drinking and related problems, such as traffic crashes.*

Although little is known about the specific mechanisms by which the density of alcohol outlets affects individual drinkers, Abbey et al. (1990) has suggested that the physical availability of alcohol influences consumption through drinkers' perceptions of alcohol availability. The importance of this social factor was illustrated in New Zealand, where consumers reported being more comfortable purchasing wine after it became available in grocery stores (Wyllie et al. in press). Despite evidence that increased density at the aggregate level is associated with higher levels of drinking, additional studies can provide insight about how individual drinkers respond to changed outlet density and whether light, medium, and heavy drinkers are differentially affected by changing outlet densities.

Legal Drinking Age

Establishing 21 years as the minimum drinking age for alcohol purchase and possession is considered a prevention measure that reduces adolescents' access to alcohol. Accordingly, the issue of a minimum legal drinking age has attracted considerable research attention, particularly after the passage of Federal legislation that provided incentives to all States to establish 21 as the minimum age for purchase and consumption of alcohol. A recent review of more than 50 studies conducted in the 1980s provided evidence that raising the legal drinking age to 21 effectively reduced youth drinking and related problems, such as traffic crashes (Wagenaar 1993). Some studies, however, have not found this prevention measure to be effective, although their results may be limited by their small study samples and problematic research designs (e.g., Allen et al. 1994; Hughes and Dodder 1992; Mooney et al. 1992).

O'Malley and Wagenaar (1991) explored the effect of changes in the legal minimum drinking age law on alcohol consumption and relevant behaviors and attitudes. The investigators examined 11 years (1976 through 1987) of data from annual nationwide probability surveys of high school seniors and followup surveys through age 24, before and after the legal drinking age was changed in dozens of States. Data on more than 15,000 youth were collected each year. Both longitudinal and cross-sectional analyses revealed that an increase in the legal minimum drinking age from 18 to 21 years was associated with a significant decline in alcohol use and a 15-percent decline in traffic fatalities (O'Malley and Wagenaar 1991). Moreover, compensatory use of marijuana did not increase when the legal drinking age made alcohol less available; if anything, marijuana use among youth also declined. Other problems frequently associated with adolescent alcohol use, such as suicides, pedestrian deaths, and other unintentional injuries, also declined after the legal drinking age was increased to 21 (Jones et al. 1992).

Despite reductions in drinking after the legal drinking age was raised, most underage youth still drink (Johnston et al. 1994). In light of this, researchers are now focusing attention on means of enforcing the drinking age and identifying sources of alcohol for underage youth. Wagenaar et al. (1993) and Wagenaar and Wolfson (1995) analyzed two data sources on liquor law violations (State-by-State data on liquor law arrests from the FBI Uniform Crime Reports and detailed data on Alcoholic Beverage Control actions against providers of alcohol to underage youth) in four States. Results revealed very low rates of enforcement of drinking-age laws, especially against those selling or providing alcohol to youth (Wagenaar et al. 1993; Wagenaar and Wolfson 1995). The few outlets cited for sales to minors were charged small penalties (median fine was $300). Enforcement of the laws varied considerably across States and across counties within States, with the level of enforcement related to several sociodemographic and enforcement attributes of the jurisdictions. Indepth interviews with commanding and line police officers revealed that procedural and political obstacles interfered with more aggressive enforcement of the legal drinking age (Wolfson et al. 1995).

Efforts to directly test the propensity of alcohol outlets to sell or serve alcohol to minors often involve having buyers who are or appear to be underage enter alcohol establishments and attempt to purchase alcohol. Several studies have shown that underage buyers are able to purchase alcohol without being asked for age verification. For example, Preusser and Williams (1992) reported that 74 percent of sales from 200 underage buy attempts in grocery stores in Albany, New York, and Washington, DC, were made to a young buyer without a request for age identification. Similarly, O'Leary et al. (1994) found that 59 percent of 46 underage buy attempts at liquor stores in a county in New Jersey were successful. Finally, Forster et al. (1994) engaged three 21-year-old women who appeared to be underage and reported that the youthful buyers were able to purchase alcohol in 47 percent of 336 buy attempts at 112 establishments licensed to sell distilled spirits, wine, and strong beer for off-premises consumption in multiple northern Minnesota communities.

Forster et al. (1995) expanded their initial study to include two purchase attempts at all outlets selling alcohol for off-premises consumption and at a randomly selected sample of 40 percent of outlets selling for on-premises consumption in selected Minnesota and Wisconsin communities. Buyers in this study, who appeared to be under the legal minimum drinking age, attempted to buy alcohol at bars, restaurants, liquor stores, and grocery stores. Of the 790 attempts at off-sale outlets, 52 percent were successful; of the 8,984 attempts at on-sale outlets, 50 percent were successful. These results suggest that underage youth can make illegal purchases of alcohol as easily at one type of outlet as the other.

Server training encompasses a wide range of programs that can be classified as awareness, server, and manager programs.

Through focus group discussions and a survey of large samples of 9th graders, 12th graders, and 18- to 20-year-olds in 15 northern Midwest communities, Wagenaar et al. (1993, 1996) have confirmed that many older youth purchase alcohol directly and that few of them use false age identification. Younger teenagers initially gain access to alcohol from the alcohol stocks kept in parents' or friends' homes. By the time teenagers enter high school, parties become an important source of alcohol and continue to be for older youth. The most common source of alcohol for underage youth, however, is a person who is of legal drinking age (Wagenaar et al. 1996).

Server Intervention, Alcohol Control Laws, and Dram Shop Liability

Efforts to reduce the incidence of injury and death to bar and restaurant patrons include a host of measures to modify alcohol service practices so that they are more responsive to the patrons' safety. These practices include training servers and trainers about responsible alcohol service policies and practices; enforcing alcohol control laws more aggressively; and using dram shop laws, which enable third parties to collect for damages caused by illegal alcohol service.

Server Training

Server training as an injury prevention measure began in the mid-1960s and coincided with increasing knowledge of the problems that can result from abusive drinking. By the 1980s, many training programs were available, and several courses were marketed nationally. Two of the most widely taught programs were Techniques of Alcohol Management, developed by the Michigan Licensed Beverage Association, and Training for Intervention Procedures for Servers of Alcohol, a privately developed program available throughout the country. Initial efforts in this area relied on management's acceptance and promotion of server training, but gradually States have become interested in implementing laws that require or encourage such training.

Server training encompasses a wide range of programs that can be classified as awareness, server, and manager programs. Awareness courses are intended primarily to introduce the topic of responsible alcohol service to key groups in communities and to generate interest in developing comprehensive server intervention programs. Server training programs, which typically are brief (running only several hours), educate waitresses, waiters, and bartenders about how to avoid selling alcohol to minors and to people who are intoxicated. Management courses provide information on policy issues and instructions on how to create a drinking environment that will minimize the possibility of problem drinking and facilitate effective server interventions when problems do occur.

Three recent studies have evaluated how programs designed to create safer serving practices may affect server behavior (Gliksman et al. 1993; Howard-Pitney et al. 1991; McKnight 1991). In one study, Howard-Pitney et al. (1991) conducted a 1-day training program for 97 servers and 43 managers from alcohol outlets in a Utah city. One month after the training, a pair of observers visited the servers' work sites to compare the responses of trained servers with those of untrained servers from matched outlets within the same city. During the work site visits, one observer ordered and consumed three alcoholic drinks in 1 hour and then ordered a fourth drink. This amount of alcohol ensured that the observer was becoming legally intoxicated. Trained servers were expected to interpret this drinking behavior as appropriate for intervention. Results showed that training increased the trainees' knowledge about responsible alcohol service and improved their beliefs that customers would appreciate server interventions to reduce risky drinking. However, the work site visits revealed that training had no effect on servers' behavior compared with that of servers in the control group (table 1). The researchers noted that outlets whose servers received training were more likely to advertise low-alcohol or nonalcoholic beverages and that there was less evidence of employees drinking on the job in these outlets. These outcomes, however, may reflect selection effects in that the outlets receiving server training were more likely to have volunteered for the training.

In a second study, McKnight (1991) conducted a 6-hour training program for 876 servers and 203 managers from 100 alcohol outlets in 8 States. Results showed that training was associated with a significant increase in observed server intervention with seemingly intoxicated patrons. Knowledge, attitudes, and self-reported behaviors related to alcohol service and server intervention also improved among trainees. Even after the program, however, interventions were observed in only 20 percent of the total 1,590 visits. Furthermore, the servers terminated service of alcohol to an intoxicated patron—as required by law in most States—in only 7 percent of the interventions.

Table 1. Mean number of interventions by servers in treatment and control establishments.

Type of Intervention	Treatment Servers (N = 22)	Control Servers (N = 19)
Communicated that server was aware of customer's drinking behavior	0.14	0.32
Slowed the delivery of drinks to the table	0.18	0.26
Suggested customer order a nonalcoholic drink or food	0.23	0.37
Offered to find transportation for an intoxicated customer	0.00	0.00
Explained that house policy does not allow the server to serve another alcoholic drink to customer	0.18	0.16
Verified that the nondrinking customer would do the driving	0.00	0.00
Refused to serve customer another alcoholic drink	0.23	0.16
Notified management if intoxicated customer became problematic	0.00	0.00
Mean of all interventions	0.95	1.26

Note: Data are based on observations by a nondrinking observer of server interventions with the drinking observation partner. Source: Howard-Pitney et al. 1991. Reprinted by permission. Howard-Pitney, B; Johnson, M.D.; Altman, D.G.; Hopkins, R.; and Hammond, N. Responsible alcohol service: A study of server, manager, and environmental impact. *American Journal of Public Health* 81(2):197–199, 1991. ©American Public Health Association.

In a third study, Gliksman et al. (1993) matched staff from eight alcohol establishments into pairs, randomly assigning one of each pair to receive a training program for managers and servers that emphasized the prevention of intoxication. After training, both knowledge about responsible alcohol service and behavior of the servers improved significantly. Measures of server behavior included servers' commenting on rate of drinking or state of a patron, delaying service, offering alternative beverages, denying service, and calling the manager. Despite encouraging results, the study was limited by the small number of outlets, managers, and servers involved and by short-term followup.

Interest in server training continues to grow (Single 1993*a,b*; Single and Tocher 1992), and some States now are moving toward required training for all commercial alcohol servers. One State in which such a policy has been evaluated is Oregon, where server training has been required since January 1987. Holder and Wagenaar (1994) performed a time-series analyses of single-vehicle nighttime car crashes in Oregon (those most likely to involve alcohol and thus a standard proxy for alcohol-related crashes) from 1976 to 1989 and found that compulsory training policy was associated with significant reductions (23 percent) in single-vehicle nighttime crashes.

Nevertheless, questions remain concerning server training, such as which types of training are most effective. Evidence suggests that short-term effects of training are modest, and little is known about the long-term effects. Policies requiring training for all servers may generate increased attention to serving practices, but the effects may dissipate over time. However, server training may serve as an important adjunct to other policies and practices (e.g., enforcement of laws prohibiting sales to intoxicated customers) and server liability that have the potential for reducing risky serving practices.

Alcohol Control Laws

State and local laws and regulations define who may serve or be served alcohol (e.g., underage or intoxicated patrons), the type of alcohol that can be sold, and the time during which alcohol can be sold. Owners and servers of licensed drinking establishments are subject to these laws, and when they violate them, they can be punished by fines and short jail terms (McKnight 1993). State and local beverage control agencies establish the conditions for issuing licenses to sell alcohol; noncompliance with beverage control laws or regulations can result in the suspension or revocation of an owner's license.

Achieving compliance with alcohol control laws can be problematic. These laws serve as deterrents only if violators perceive that they will be apprehended or prosecuted for their actions. Yet, enforcement can be costly and time consuming because it requires long hours of surveillance by police officers so that they can witness a violation as it occurs in an establishment.

McKnight and Streff (1993) explored the effectiveness of increasing the level of visibility of enforcement and the rigorousness of prosecution for alcohol control laws. In this study, plainclothes police officers visited bars and restaurants in a Michigan county over a 1-year period to observe whether clearly intoxicated customers were being served alcohol. Managers and servers were notified of the enforcement effort in meetings before the start of the program and through postvisit surveillance reports. Newspaper reports of penalties imposed on alcohol servers and establishment owners who violated control laws provided additional visibility to the effort. The researchers noted that after the enforcement began, arrests for driving under the influence of alcohol related to service at bars and restaurants declined from 32 to 23 percent. Moreover, service to researchers posing as intoxicated patrons declined initially from 84 to 47 percent but then rose to 58 percent over the next few months.

Dram Shop Liability

Dram shop, or server, liability refers to the legal responsibility of an alcohol server for the damage that intoxicated patrons may inflict on themselves or others. The financial loss that bar and restaurant servers and managers may incur from these laws is thought to deter serving practices that can increase a patron's risk for a motor vehicle crash. Dram shop liability emerged through common law, case law, and statutory law long before researchers began to explore its potential effectiveness in preventing alcohol problems (Saltz 1993). Some 26 major dimensions of legal liability have been identified, and examination of statutory and case law in the 50 States reveals wide variability in the extent of liability exposure (Holder et al. 1993). Increasing focus on liability issues in both alcohol trade journals and general newspapers is associated with a higher prevalence of liability insurance in alcohol establishments (Holder et al. 1993). However, these findings represent analyses of data from only a few States and result from low response-rate nonprobability surveys of alcohol establishments.

Wagenaar and Holder (1991*b*) studied the deterrent effects of two dram-shop lawsuits filed in Texas in the 1980s on server behavior. Before the lawsuits, Texas alcohol establishments had little liability for the consequences of their alcohol beverage services. In an analysis of 1978–1988 time-series data from Texas and the other 47 contiguous States (which served as controls), the researchers found that after the publicity of the court cases, single-vehicle nighttime car crashes in Texas declined 6.5 percent in 1983 and 5.3 percent in 1984. This study suggests that a sudden change in liability exposure may affect the behavior of persons who serve alcohol. Additional research in this area can provide insight into how changes in the legal system are perceived by alcohol servers, what specific changes in server behavior occur, and whether those behavior changes affect the drinking practices of patrons.

Alcohol Warning Efforts

Research on Alcohol Warning Labels

Beginning in 1989, Public Law 100–690 (1988) required containers for alcoholic beverages to be labeled with a "clear, nonconfusing" warning of alcohol-related hazards, which reads

> **GOVERNMENT WARNING:** (1) According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. (2) Consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause health problems.

Studies of warning label issues include (1) surveys addressing label awareness, knowledge of risks, relevant beliefs and attitudes, and self-reported behavior and (2) laboratory experiments testing various types of labels and different modes of exposure to the warnings. Several studies have reported increasing awareness of the labels over time. For example, quarterly surveys of Utah residents in 1989 and 1990 found increasing awareness of the label in all subgroups but no change in perceptions regarding the risks of alcohol use or self-reported drinking behavior (Mayer et al. 1991; Scammon et al. 1991).

Mazis et al. (1991) conducted a series of nationwide random-digit dialing telephone surveys in 1989 (before the labeling law) and 1990 (after the labeling law). The 1990 survey results revealed that 35 percent of respondents said it was likely that alcoholic beverage containers had a warning, yet only 11 percent of the respondents were able to identify a specific warning label (Mazis et al. 1991). In addition, the proportion of respondents who thought that alcohol was "very harmful" increased only slightly between 1989 (prelabel) and 1990 (postlabel), with greater increases in risk perception among young, higher socioeconomic status, and heavy-drinking respondents. Nondrinkers (those who had not consumed alcohol in the past 14 days) tended to perceive alcohol as more harmful than did drinkers. Unfortunately, the Mazis study was limited by a response rate of only 40 percent.

Similar nationwide random-digit dialing surveys by the Alcohol Research Group in 1989, 1990, and 1991 had response rates of 62 to 65 percent (Greenfield et al. 1993; Greenfield and Kaskutas 1993; Kaskutas and Greenfield 1992). In 1990, 6 months after labels were implemented, 21 percent of respondents said they had seen the warning label; this figure increased to 27 percent 18 months later in the 1991 survey (Greenfield et al. 1993; Kaskutas and Greenfield 1992). The highest rates of label recognition were among higher risk target groups, namely, heavy drinkers (44 percent in 1990 and 54 percent in 1991), women aged 18–39 years (27 percent in 1990 and 35 percent in 1991), and young men aged 18–29 years (36 percent in 1990 and 48 percent in 1991) (Kaskutas and Greenfield 1992). The surveys showed that no significant changes occurred over time in knowledge of the health risks mentioned on the label or in reports of drunk driving, but the prevalence of conversations about drinking and pregnancy increased after the label law took effect.

Through random-digit dialing telephone surveys conducted before and after the introduction of warning labels on alcoholic beverages, Parker et al. (1994) determined that people in general, and those in at-risk drinking and driving subgroups, had seen and could recall the content of the warning labels. Moreover, they found evidence of respondents' attitudinal changes concerning risk assessment of drinking and driving (after two drinks) and the negative public health outcomes that are associated with alcohol abuse and referred to in the warning labels. The investigators found, however, that all respondents, and particularly those at risk for drinking and driving, reported decreased support for government regulations of alcohol sales, advertising, and production after the introduction of alcohol warning labels. The investigators suggest that this public opinion "backlash" indicates the complexity of this approach.

In addition to nationwide surveys, several studies have focused on specific population samples to gain a better understanding of the effects of warning labels on special populations. Hankin et al. (1993*a,b,c*) surveyed urban African-American pregnant women receiving care at a Detroit area prenatal clinic and found that, although the warning label law was implemented in November 1989, awareness of the label did not begin to increase significantly until mid-1990. Within the population studied, drinkers of beer and wine-coolers and women under age 30 were more likely to report label awareness. As awareness of the label increased in mid-1990, reported drinking declined slightly among light-drinking pregnant women, but there was no change among heavier drinkers (defined in this study as women who consumed at least 0.5 ounce of absolute alcohol per day at the time that they became pregnant) (see Chapter 6, Effects of Alcohol on Fetal and Postnatal Development, for a discussion of drinking among pregnant women and alcohol-related birth defects).

Surveys conducted in 1990 and 1991 among Hispanics in San Francisco showed that awareness of the warning label increased during the 1-year period (Marin

1994). However, fewer than one-third of the respondents reported that they were aware of warnings on beer and wine containers.

To determine the effect of alcohol warning labels on youth, MacKinnon et al. (1993) surveyed grade 12 students in Marion County, Indiana, 1 year before and 1 year after the implementation of the warning label law. Label awareness among respondents increased from 19 percent before to 43 percent after the warning labels appeared on alcoholic beverage containers; heavier drinkers were more aware of the warnings than were light drinkers (MacKinnon et al. 1993). No substantial changes occurred, however, in alcohol use or in beliefs about the risks mentioned in the warning.

In summary, the studies described above demonstrate that awareness of the warning labels increased over time. Regular drinkers, having greater exposure to container labels, were more likely than other drinkers to be aware of the newly added labels. The observed effects of the current warning label on risk perceptions and drinking practices, however, were modest.

Supplementing beverage container warnings with warnings in print and broadcast advertisements is likely to improve dissemination of the warning information significantly.

The modest effects of alcohol warning labels may result from the use of labels that fail to follow established principles of effective warning design. Although the current label highlights the two effects of alcohol that have been found to be most believable—birth defects and driving impairment (Andrews et al. 1990, 1991, 1993)—it lacks certain basic features that could make it more eye catching.

In three experiments, Laughery et al. (1993) showed which warnings labels are noticed more quickly: those printed on the front of a container rather than elsewhere, those printed horizontally, and those printed with a red pictorial warning. These simple features of warning labels increased their being noticed by 37 percent, and the use of a pictorial alone increased notice by 21 percent. A feature that is included on many current containers, a border around the warning, has little effect on drawing attention to the warning (Laughery et al. 1993).

The words used in a warning label also are important. The results of two experiments with alternative wording (MacKinnon 1993) indicated that the current warning leads some subjects to avoid the product but that stronger words generate significantly higher avoidance than softer words, including "*may* cause health problems" and "pregnant women *should* not drink."

Warnings in Advertisements

Recent research has shown that the placement of warnings in both print and broadcast advertisements increases public knowledge of alcohol risks. For example, in an experiment exposing 105 introductory psychology students to various warnings positioned in print and television advertisements for alcoholic beverages, Barlow and Wogalter (1993) found that warnings in a magazine advertisement had significant effects on the students' knowledge and memory of alcohol hazards. The most conspicuous warnings had the most effect. Similarly, television advertisement warnings significantly increased the students' knowledge of alcohol hazards, especially when the warnings were visual and auditory.

In another study, Slater and Domenech (1995) randomly assigned 75 college students to exposure to four alcohol warnings inserted in randomly sampled television beer advertisements. Limited short-term exposures to the warnings resulted in the students' decreased confidence in what were generally positive assessments of the benefits of beer consumption. The investigators noted that college students have strongly embedded beliefs about alcohol and that reducing positive perceptions of alcohol is a likely precursor to belief change among persons in resistant populations.

Further information on how best to design alcohol warnings in advertising has emerged from an experiment testing the effects of low-severity warnings versus high-severity warnings in television advertisements using audio or video delivery modes (Smith 1990). Most subjects recalled the warnings only when they were delivered via audio or by combined audio and video modes, but the video-only warning was not noticed. The more severe warning produced higher recall.

In summary, supplementing beverage container warnings with warnings in print and broadcast advertisements is likely to improve dissemination of the warning information significantly. The delivery of strong, conspicuous warnings in a combined audio and video mode appears most effective.

Prevention in the Workplace

In addition to broader community and policy environments that affect drinking and provide important avenues for preventive intervention, particular settings, such as the workplace, can be the focus of prevention programs. There appears to be a high degree of ambivalence in the United States toward establishing and enforcing an alcohol-free workplace, although studies on which such a conclusion might be based are typically limited to one or just a few plants (Ames 1990; Ames and Janes 1990, 1992; Janes and Ames 1993). Factors that apparently facilitate drinking are informal rather than written standards, low supervision and lack of visibility of work and worker, perceptions that alcohol is easily available in and around the workplace, and workplace stress and alienation that may contribute to drinking (Ames and Janes 1992).

Indepth ethnographic interviews and surveys in one durable-goods manufacturing plant revealed that most supervisors and managers in key decisionmaking roles did not know whether their organization had a formal alcohol policy (Ames et al. 1992). The vast majority of the plant's hourly and salaried workers (89 and 94 percent, respectively) said it was easy or very easy to bring alcohol into the workplace. More than 80 percent of both groups said it was unlikely that a person who had one or two drinks in the plant would be caught. Among hourly workers, 69 percent said that a supervisor would do nothing or would just talk to an employee who occasionally drank on the job.

Even among health organizations, there are few formal policies on alcohol in the workplace (Braddick 1993). Ames and Delaney (1992) and Ames et al. (1992) contend that the role of the supervisor is central to preventing alcohol problems in the workplace. Supervisor inaction, pressure from unions to avoid disciplinary action, and ambiguity between two streams of workplace policy (alcohol-related disciplinary action versus employee assistance programs to treat workers with alcohol problems) all limit the effectiveness of prevention efforts. Overcoming these barriers to prevention requires management's careful assessment of the costs of drinking, identification of workplace-specific risk factors, sharing of this information across management and labor sectors, and consensus building for action (Ames 1993).

Ames (1993) has suggested that a comprehensive plan for preventing alcohol problems in the workplace should include primary, secondary, and tertiary prevention approaches. Primary prevention approaches aim to identify and manage environmental risk factors that lead to unhealthy drinking patterns. Secondary prevention approaches aim to detect and diagnose alcohol problems at early stages. Tertiary prevention approaches aim to ameliorate, treat, or cure chronic alcoholism.

Prevention of alcohol-related problems often is accomplished in the workplace when employees seek help from or are referred by a supervisor to an employee assistance program (EAP). An EAP is a work site-based program that, within the scope of its functions, can offer support and rehabilitation for employees who are identified as alcoholics (considered a tertiary prevention) or can provide information so that an employee who is abusing alcohol becomes aware of the risks of his or her drinking and agrees to take measures to prevent further progression of the drinking problem (considered a secondary prevention). A comprehensive plan for preventing alcohol use and abuse in the workplace must include primary prevention approaches as well. According to Wallack and Winkleby (1987), primary prevention in the workplace has three dimensions: health promotion (which focuses primarily on healthy persons and provides information and skills that enhance healthier lifestyles), disease prevention (which identifies "at-risk" groups of employees and provides special services to avert problems before they occur or progress), and health protection (which promotes direct change or regulatory measures and potentially can reach all employees in a given setting). An EAP may perform activities that can be categorized in the first two dimensions, in the form of alcohol educational services for employees and their families and stress-management training (Blum and Bennett 1990) or by a Health Promotion Program sponsoring health-risk appraisals and recreational activities (Erfurt 1990).

Roman and Blum (1992) evaluated data on 6,400 employees from multiple and varied work sites who used EAPs during a 2-year timeframe (early 1990 to mid-1992), comparing characteristics of persons who were referred to EAPs because of alcohol problems with those without alcohol problems. The investigators found that the two groups of clients did not differ in terms of supervisory or employee training responsibilities or in their responsibility for making significant job-related decisions. Job characteristics of clients who had alcohol problems, however, did differ from those of other clients: Clients referred for alcohol problems were more likely to work as outside representatives of the organization, have opportunities to work off the premises, travel as part of their jobs, routinely work overtime hours, use motor vehicles, or operate heavy equipment. Legal problems as well as warnings from supervisors about job attendance and job performance also were more common among these clients. In fact, supervisors and spouses played a significant role in the referral process for clients with alcohol problems, suggesting that family and workplace act together to influence such employees to seek help.

Prevention of Drinking and Driving

Traffic crashes are the leading cause of death for persons under 35 years of age and are the fifth leading cause of death across all age groups (National Center for Health Statistics 1994). About 45 percent of all traffic crashes are associated with alcohol use (National Highway Traffic Safety Administration 1994). The estimated total cost of alcohol-related traffic crashes in the United States, $148 billion annually, represents $1.09 in external costs for each drink consumed (Blincoe and Faigin 1992; Miller and Blincoe 1994).

The estimated total cost of alcohol-related traffic crashes in the United States, $148 billion annually, represents $1.09 in external costs for each drink consumed.

Several prevention approaches can be taken to reduce the incidence and severity of alcohol-related traffic crashes. For example, an approach conceptually may focus on improving driving safety. Placement of airbags in cars and efforts to increase the proportion of drivers who use safety belts improve driving safety and thus decrease the likelihood of severe injury. Also, prevention efforts may directly target the prevalence of alcohol-impaired driving by preventing individuals who have consumed alcohol from driving. Finally, lowering the level of alcohol consumption by the population can diminish the rates of alcohol-related traffic crashes.

Researchers have examined several approaches to determine their effectiveness in preventing drinking and driving. Designated driver programs, enforcement of impaired-driving laws, lower allowable BACs for young drivers, and deterrence measures are discussed below.

Designated Driver or Safe-Ride Programs

The designated driver, or safe-ride programs, is a heavily promoted approach to preventing alcohol-impaired driving; however, it has not been well evaluated (DeJong and Wallack 1992; Wagenaar 1992). Shore and Sanchez (1993) assessed one program, the Wichita Ride Service Program, which operates from Thanksgiving to January 2 each year. The service provides free taxi rides to individuals who appear to be intoxicated. Based on observations of participating cab drivers, the authors estimated that three-fourths of the 123 individuals who used the service during the 1989–1990 season were young males and that one-third appeared extremely intoxicated. These riders had cars and could have driven themselves if the service was not available. The investigators suggest that the population at risk for impairment used the program.

Shore et al. (1991) investigated the use of designated drivers among fraternity members at a large midwestern university. Members of two fraternities agreed to designate a driver any time three or more members went out and to complete a questionnaire after each event. Data from one fraternity were excluded because the students were not truthful on the questionnaires. Data from the other fraternity indicated that even after agreeing to designate drivers, many members forgot to do so, and when they did remember, the designated drivers typically still consumed alcohol, although at less than usual rates. The authors also observed that despite participants having favorable attitudes about the concept of a designated driver, they experienced practical problems with the approach that may limit its use.

Designated driver or safe-ride programs may help to change the normative environment in which alcohol-impaired driving is acceptable, and they do remove some impaired drivers from the road. However, further evaluation is needed to identify the potential costs and benefits of these programs. Groups most likely to designate drivers (e.g., married couples) may be at the lowest risk for alcohol-related crashes. Furthermore, being a designated driver may be unappealing to some people. Problem drinkers often go to bars by themselves, making use of the approach problematic. Finally, additional research can confirm whether these programs encourage alcohol consumption among passengers. If so, an unintentional increase in alcohol consumption among nondrivers could lead to an elevation in other public health problems associated with alcohol drinking (DeJong and Wallack 1992; Wagenaar 1992).

Enforcement of Impaired-Driving Laws

Increased enforcement of impaired-driving laws is another means to reduce the problem of alcohol-impaired driving in the general population. Stronger enforcement concomitant with appropriate publicity campaigns can achieve general deterrence, based on the perception that an infraction of the law will result in a penalty. The severity of consequences is less important than a sure, swift penalty in deterring alcohol-impaired driving (Nichols and Ross 1990; Ross 1992).

To increase the perceived risk of being detected when driving after drinking, law enforcement officials can use sobriety checkpoints, at which all or a random sample of cars are stopped and checked for drinking drivers. In a comprehensive meta-analysis of the 1960–1991 research literature on the effects of policies on alcohol-impaired driving, Wagenaar et al. (1995) identified sobriety checkpoint programs accompanied by publicity campaigns to be effective in reducing alcohol-impaired driving and traffic crashes.

Evaluating a roadside checkpoint program in New Jersey, Levy et al. (1990) found a slightly lower incidence of single-vehicle nighttime crashes immediately after the program started. Two years later, its effects were substantial (i.e., 30 percent reduction in car crashes). In contrast, an educational program targeting alcohol-impaired drivers was associated with a 24-percent decrease in crashes the first month of the program, but the effect diminished to less than a 1-percent reduction 3 years after the program began. Thus, the effectiveness of checkpoint enforcement increased the longer it was in place, whereas the effectiveness of education programs dissipated over time.

> *In recent years, many States have lowered allowable BACs for young drivers in an effort to reduce the involvement of young drivers in alcohol-related crashes.*

In a time-series analysis, Homel (1994) noted that after a sobriety checkpoint policy was implemented in New South Wales, Australia, fatal crashes declined by 20 percent overall and by 30 percent during holiday periods. This experience illustrates the sizable preventive effect of a rigorously implemented alcohol-impaired driving checkpoint program.

Sobriety checkpoints may be less effective if drivers believe that illegal levels of alcohol consumption cannot be detected even if they are stopped by the police. Detecting lower BACs in impaired drivers can be especially difficult if left to observation alone. Passive alcohol sensors enable law-enforcement agents to screen drivers for elevated BACs without touching the driver. Foss et al. (1993) investigated the accuracy and validity of passive alcohol sensors and found that they could identify BACs over 100 mg/dL (the legal limit in most States) in 80 percent of the cases in which they were used. In New South Wales, the success of the checkpoint program was achieved by testing every driver stopped, whereas at many U.S. checkpoints, officers attempt to detect alcohol impairment by talking briefly with the driver. Passive alcohol sensors might be important in such situations, to increase motorists' perceptions that they will be detected if they drive after drinking.

Lower Allowable BACs for Young Drivers

In recent years, many States have lowered allowable BACs for young drivers in an effort to reduce the involvement of young drivers in alcohol-related crashes. The new BACs for youth vary by State, ranging from 0.00 to 0.05 percent. In an analysis of fatal crashes in the first four States to implement lower BAC limits (Maine, New Mexico, North Carolina, and Wisconsin), Hingson et al. (1991) examined nighttime fatal crashes, comparing young and adult drivers within each State and pairing each State with a comparison State that had not implemented a lower BAC limit for youth. Across the four States, nighttime fatal crashes involving young drivers declined by 34 percent after the implementation of the lower BAC limits for youth, compared with a 7-percent decline among adults. However, there was also a 26-percent decline among youth in the comparison States, suggesting that only the difference (34 percent less 26 percent, or 8 percent) was attributable to the lower BAC policy. A series of statewide surveys in Maine revealed that many teens did not know that they could lose their licenses for 1 year if they drove after drinking. Thus, Hingson (1993) suggested that implementation of a strong educational program along with the law may have improved the law's effectiveness.

In a more recent study, Hingson et al. (1994) assessed the effect of lower legal BACs for young drivers in the 12 States that had implemented such a law before 1991 (table 2). The investigators observed that during the postlaw period, the proportion of fatal single-vehicle nighttime crashes declined 16 percent among young drivers. In 12 neighboring comparison States, crashes in

Table 2. Proportion of fatal crashes that involved single vehicles at night among teens.

States	Before	After	Percent Change
.00 Law			
North Carolina	0.313	0.215	Down 31
Wisconsin	0.335	0.271	Down 19
Oregon	0.240	0.263	Up 10
Arizona	0.259	0.254	Down 2
.02 Law			
Maine	0.407	0.291	Down 29
Maryland	0.317	0.300	Down 5
Ohio	0.218	0.184	Down 16
Vermont	0.375	1.000	Up 167
.04–.06 Laws			
New Mexico	0.299	0.294	Down 2
California	0.241	0.220	Down 9
Rhode Island	0.083	0.250	Up 201
Georgia	0.204	0.217	Up 6
Total	0.289	0.242	Down 16
Comparison			
Virginia	0.341	0.316	Down 7
Minnesota	0.285	0.264	Down 7
Washington	0.175	0.256	Up 46
Utah	0.231	0.277	Up 20
Massachusetts	0.395	0.364	Down 8
Pennsylvania	0.278	0.341	Up 23
Indiana	0.142	0.188	Up 32
New Hampshire	0.333	0.375	Up 13
Colorado	0.253	0.256	Up 1
Texas	0.271	0.285	Up 5
Connecticut	0.379	0.296	Down 22
Alabama	0.238	0.235	Down 1
Total	0.299	0.303	Up 1

Source: Hingson et al. 1994.

the same category rose by 1 percent. The investigators also observed that the lower the allowable BAC, the more profound the effect. Fatal single-vehicle nighttime crashes declined 22 percent among drivers in States with 0.00 percent limits, whereas the rate declined only 2 percent among drivers of the same age in comparison States. A smaller decline (17 percent) occurred in States with 0.02 percent BAC limits, and no difference appeared between States that lowered BAC limits to the range of 0.04 and 0.06 percent relative to comparison States.

Specific Deterrence

Controlling alcohol-impaired driving also involves specific deterrence, or approaches that aim to prevent drivers with a record of drinking and driving from repeat offenses. An example of a specific deterrence is the interlock device, which can be installed in the cars of people convicted of alcohol-impaired driving. These devices require that the driver pass a dexterity or an alcohol-free breath test before the vehicle will start. Morse and Elliott (1992) compared the rates of recidivism for individuals who have had their driver's license suspended and those who have had license suspension in addition to an interlock device installed in their cars. The investigators found that drivers using the interlock were less likely to repeat the alcohol-impaired driving offense within 30 months compared with those who only had their license suspended. Maximum benefits were achieved when the interlock device was installed immediately after the conviction and remained in place for at least 12 months. The reduction in the re-arrest of alcohol-impaired drivers was less for drivers who had the interlock device for only 6 months (Elliott et al. 1993).

Despite documented success with the interlock device, some judges are unwilling to require the ignition devices. Moreover, when devices are ordered, enforcement is needed to ensure that the devices are actually installed and that individuals do not bypass the interlock system (Baker and Beck 1991; Elliott et al. 1993).

Active and visible police enforcement is essential for effective drinking and driving deterrence. Enforcement of preventive measures is more common in communities with lower rates of other serious crime and in communities whose police officers have a high level of professionalism (Weiss 1991). Arrests for alcohol-impaired driving also vary widely among police officers. A study of officers from 19 departments in Pennsylvania found that one-half of all arrests for driving under the influence (DUI) were made by only 10 percent of the officers (Mastrofski et al. 1994).

The swiftness and certainty of punishment for arrested DUI offenders depend on the court. To increase the efficiency of the court system, Russillo (1992) recommends establishing in each State a central data system for gathering and sharing information. Moreover, because funding and other available resources can affect the ability of the judicial system to provide speedy trials, Russillo (1992) and Ross (1991) recommend reducing caseloads by increasing administrative rather than criminal penalties.

Penalties also can vary from one court to the next as a result of plea bargaining and the discretion of the judges, particularly in cases for which the length and severity of criminal penalties are not mandated by law. To ensure the courts' consistent application of full penalties for

DUI convictions, citizen groups may monitor the courts during the adjudication of DUI cases. After reviewing studies of the effects of court monitoring, Shinar (1992) concluded that although the studies suffered from some methodological problems, there was evidence that citizen court monitoring could increase the probability of a DUI conviction.

Informal Deterrence

Informal deterrence refers to situations in which friends, family, or strangers intervene to prevent someone from driving while impaired. These interventions include threatening negative sanctions (e.g., calling the police), offering to provide a ride home, or physically preventing the person from driving (e.g., taking away the car keys). To assess levels of informal social control, Collins and Frey (1992) surveyed 195 students (aged 17–60 years) in an introductory sociology course at a southwestern university and found that 83 percent had attempted to stop someone from driving after drinking. Of those who attempted to intervene, 74 percent reported success.

> *The contributory role of alcohol to violence may be neither direct nor simple.*

Reducing Alcohol Consumption

Although prevention approaches that reduce the probability and severity of traffic crashes and the prevalence of alcohol-impaired driving are essential and effective, they can be even more effective when combined with strategies to reduce alcohol consumption. Extensive research indicates that reducing the availability of alcohol (e.g., by raising the minimum drinking age, increasing excise taxes, and maintaining State liquor monopolies) is effective in lowering alcohol consumption and ultimately in decreasing the number of alcohol-related traffic crashes (Moskowitz 1989*b*; Toomey et al. 1993). Reducing levels of alcohol consumption in the general population may also decrease the morbidity and mortality related to other public health problems (e.g., suicides, homicides, assaults, and other unintentional injuries) that are frequently associated with alcohol use (Baker et al. 1992).

Prevention of Violence

In recent years, violence has been an increasing concern in communities across the United States. Public health researchers have started to identify risk factors that might be modified to reduce rates of violence. Research, past and present, clearly demonstrates a positive association between alcohol consumption and various forms of violence. An estimated 50 percent of both victims and perpetrators of violence use alcohol (Lenke 1990; Rosenberg and Fenley 1991), and the consistency of this association across countries, demographic subgroups, and types of violence (e.g., homicides, suicides, and sexual assaults) suggests that the association is not spurious. Various studies have reported that adult men and younger men and women continue to be more likely to have consumed alcohol before a violent incident (Clayton and Webb 1991; Meyers et al. 1990). Heavier drinkers may be most at risk for being involved in violence (Cherpitel 1993; Muscat and Huncharek 1991), and those who consume some alcohol are more at risk than those who consume no alcohol at all (Goodman et al. 1991). Indeed, a high percentage of both victims and perpetrators of violence drink alcohol before a violent assault (Frintner and Rubinson 1993; Muscat and Huncharek 1991). Although many violence studies to date have important methodological limitations (e.g., limited geographic sampling or limited study populations), results consistently indicate the pervasiveness of alcohol use in violent situations—an association that exists across countries, time, and methods of research.

However, the degree to which alcohol *causes* violence versus simply being a concomitant factor remains unresolved (see Chapter 7, Effects of Alcohol on Behavior and Safety). The contributory role of alcohol to violence may be neither direct nor simple (Pernanen 1993). More likely, alcohol-related violence is the result of interaction between individual factors and environmental factors that either promote or inhibit violence, such as the availability of a weapon or the presence of peers who encourage violence (Clayton and Webb 1991; Parker 1993; Taylor and Chermack 1993). Additional research is needed to identify the exact nature of the role of alcohol in violence.

Several experimental studies reviewed by Taylor and Chermack (1993) lend support to the theory that environmental factors influence alcohol-related violence. Research shows that in a laboratory setting, intoxicated subjects are more aggressive (i.e., more willing to administer a stronger shock) than those who received a placebo or drank no alcohol. Situational factors (e.g., information that an adversary is going to cause physical harm and social pressure to be violent) further increase alcohol-related aggressiveness.

Social policies that discourage alcohol use appear to reduce rates of violence. Cook and Moore (1993) examined the effects that increasing State beer excise taxes might have on rates of homicides, rapes, assaults, and robberies. Using data from 1978 to 1988 in econometric time-series analyses, the researchers found that each 10 percent increase in beer taxes reduced homicides by 0.3 percent. Rapes were down 1.32 percent; assaults, 0.3 percent; and robberies, 0.9 percent. However, interpretation of these findings is compromised because this study omitted important variables, such as poverty, racial composition, regional differences, and deterrence measures (Parker 1993). The study therefore should be viewed as offering preliminary evidence that policies aimed at reducing aggregate alcohol consumption are effective in decreasing rates of violence.

Social policies that discourage alcohol use appear to reduce rates of violence.

Altering environmental conditions that interact with alcohol consumption may also help to reduce alcohol-related violence. For example, researchers found that the violence rate was high in pubs and clubs in Sydney, Australia (Homel et al. 1992). The levels of violence were higher in establishments that had aggressive bouncers, less exciting or poorer quality bands, uncomfortable settings (crowding, loud music, poor ventilation), and lack of available food after midnight. More research is needed to assess whether similar conditions are related to violence in other countries in establishments that serve alcohol and whether changing these conditions is effective in decreasing the incidence of violence.

Community Prevention Studies

Variations in alcohol use across communities cannot be explained fully in terms of known individual characteristics (Curry et al. 1993) (table 3). Community structures, institutions, and policies affect drinking and risk for alcohol problems. Thus, it is unlikely that strategies involving single interventions directed solely at the individual can reduce alcohol problems (Holder and Giesbrecht 1990; Saltz 1988). The social, political, and economic factors that collectively can encourage problem drinking also should be considered in prevention efforts (Hyndman et al. 1992).

This need is addressed by an increasing number of multifaceted community-based alcohol prevention efforts (Saltz 1988). Community research and demonstration programs designed to prevent alcohol problems emulate to some extent the large-scale community intervention projects designed to reduce risks for cardiovascular disease in the 1980s. Both types of projects typically compare results from "experimental" geographic regions, where programs are implemented, and "control" regions, where programs are not undertaken. In addition, approaches in both disciplines employ multilevel prevention approaches that address a range of populations and risk behaviors. Although the effects of cardiovascular risk-reduction projects have not been fully evaluated, various researchers have reported equivocal findings about the projects' benefits (Farquhar et al. 1990; Luepker et al. 1994; Shea and Basch 1990). Yet, for alcohol researchers, the literature on cardiovascular prevention programs provides much information about the advantages and complications of large-scale, community-oriented prevention research (Giesbrecht et al. 1993).

Since 1990, community prevention efforts focusing on alcohol have received increasing attention. Numerous reports have discussed the importance of community mobilization efforts, describing innovative programs, analyzing the complexities of implementing and evaluating such interventions, and identifying barriers to community change (Casswell and Stewart 1990; Delewski and Saltz 1990; Giesbrecht et al. 1990*a*; Greenfield and Zimmerman 1993; Hennessey 1991; Manger et al. 1992). Helpful guidelines for working with special populations (e.g., Native Americans and Hispanics) also are available (Bogan 1990; May 1992).

Several communitywide alcohol prevention projects for which full evaluations are available have achieved significant effects on awareness, public support for alcohol prevention, and related attitudes. However, the changes in drinking behavior or the prevalence of alcohol-related problems appear to be temporary for many of these projects (Gorman and Speer in press; Hyndman et al. 1992; see table 3).

Three important multicommunity alcohol prevention trials currently are under way. One of the trials, Project Northland (discussed earlier), is a randomized trial that

Table 3. Summary of community-based alcohol use prevention programs.

<table>
<tr><th>Study</th><th>Rationale and Design</th><th>Principal Theoretical Framework</th><th>Intervention Strategies</th><th>Planning Process</th><th>Evaluation Methods</th></tr>
<tr><td>California "Winners" Project (Barrows and Wallack 1982/83)</td><td>To assess the combined effects of a community program and mass media intervention on program awareness, knowledge, attitudes, and behavior</td><td>Social marketing, and values-behavior model</td><td>Mass media, community meetings, and school curriculum</td><td>Little coordination of program components</td><td>Household surveys conducted in three communities (community intervention, mass media, comparison) at three points in time</td></tr>
<tr><td colspan="6">Summary of Results. The intervention led to increased awareness of the program and some gain in knowledge but had no effect on attitudes or behavior.</td></tr>
<tr><td>Midwestern Prevention Project (Pentz et al. 1989<i>a</i>)</td><td>To reduce alcohol use through a school-based curriculum and supportive parent, media, community, and policy components</td><td>Social learning theory</td><td>Skills-based school curriculum, mass media, parent program, community organization, and policy initiatives</td><td>10-stage implementation process</td><td>Surveys conducted with students who received the program (intervention group) and those who did not (comparison group)</td></tr>
<tr><td colspan="6">Summary of Results. A greater proportion of the comparison group reported alcohol use at 1-year followup. However, this difference was not maintained at the 3-year followup.</td></tr>
<tr><td>Community Action Project (Casswell and Gilmore 1989)</td><td>To reinforce moderate drinking and influence policies related to alcohol availability through community organizing and the mass media</td><td>Education for critical consciousness</td><td>Community organization and mass media</td><td>Coordination of the project through regular meetings of research team and community organizers</td><td>Random surveys conducted at two points in time in three communities (community organizing plus mass media, mass media only, and comparison)</td></tr>
<tr><td colspan="6">Summary of Results. The interventions had limited impact and operated primarily in inhibiting the trend toward greater liberalization of attitudes toward alcohol evident in the comparison community.</td></tr>
<tr><td>Vermont Self-regulation Project (Worden et al. 1989)</td><td>To reduce alcohol-impaired driving through self-regulation training (SRT)</td><td>Skills training with community support</td><td>Drink calculations distributed through licensed outlets</td><td>Recruiting all licensed outlets and training their staff</td><td>Pretest/posttest surveys of drivers in three communities (SRT, PSAs, comparison)</td></tr>
<tr><td colspan="6">Summary of Results. Drinking behavior remained the same in all three communities. There were fewer subjects with BACs above the legal limit in the SRT community at posttest than in the other two communities.</td></tr>
</table>

focuses on reducing drinking among 10- to 14-year-olds and includes the combination of school curricula, peer leader programs, parent involvement and education, and community task forces in 10 interventions. Ten control communities also are involved in the study. Initial results show a lower prevalence of alcohol use among students in the intervention schools after a 3-year exposure to the program (Perry et al. in press). Whether these reductions will be maintained as the adolescents move into the high-risk middle-teen years is unknown pending further followup.

The second trial, the Communities Mobilizing for Change on Alcohol Project, is a randomized 15-community trial designed to change institutional structures, organizational practices, and public policies to reduce the accessibility of alcohol to youth aged 15 to 20 years (Wagenaar and Perry 1994). Baseline data reveal the ubiquity of illegal sales to minors (Forster et al. 1995) and the ease with which underage youth obtain alcohol (Wagenaar et al. 1996). Outcome data on the effectiveness of this community-organized intervention are not yet available.

Table 3. Summary of community-based alcohol use prevention programs *(continued).*

Study	Rationale and Design	Principal Theoretical Framework	Intervention Strategies	Planning Process	Evaluation Methods
Rhode Island Community Project (Putnam et al. 1993)	To assess the effect of a program targeting knowledge, attitudes, and behavior of liquor servers and police officers on a community's alcohol-related problems	Enabling theory	Server and police training, political support, and mass media	Ad hoc—intervention was to be based on needs assessment, which was not conducted	Time-series data pertaining to arrest rates and emergency room injury rates collected in three communities (one intervention and two comparisons)
Summary of Results. Alcohol-related arrests increased while alcohol-related emergency room visits decreased. However, multiple rival hypotheses compete with claims that the program was responsible for these effects.					
Tri-community Prevention Project (Giesbrecht et al. 1990*b*)	Targeted heavy drinkers to reduce average consumption communitywide	Distribution of consumption model	Mass media, community forums, individual counseling, and server training	Insufficient attention given to involving the community	Household surveys conducted at two points in time, and 8 years of time-series data pertaining to alcohol sales and hospital treatment collected from three communities (one intervention and two comparisons)
Summary of Results. Individuals in the counseling program reduced their alcohol consumption, but no noticeable decline in drinking was found in the community.					
Thunder Bay Project (Gliksman et al. 1990)	To assess the effects of reducing alcohol availability	Distribution of consumption model and social marketing	Mass media and change in municipal policies	Project designed by researchers and city officials, with community involvement in the policy initiatives	Pretest/posttest household survey conducted in two communities (intervention and comparison)
Summary of Results. Awareness and behavioral intentions moved in the direction targeted by the program, but alcohol consumption was unchanged.					
Boys & Girls Clubs Stay SMART Program (St. Pierre et al. 1992)	To reduce drug use through a skills-based curriculum delivered in a youth club setting	Social learning theory	Life skills training curriculum and booster sessions	Recruited only clubs with organizational structure capable of sustaining the project	Pretest/posttest surveys of youth in three types of study conditions (program only, program plus booster sessions, and comparison)
Summary of Results. There were small effects in changing alcohol-related behavior and small effects in perceived benefits of alcohol consumption.					

Source: Gorman and Speer in press. Preventing alcohol abuse and alcohol-related problems through community interventions: A review of evaluation studies. *International Review of Health Psychology.* Gorman, D.M., and Speer, P.M. © Copyright. Reprinted by permission of John Wiley & Sons, Ltd.

The third trial is quasi-experimental and involves six communities (three intervention, three comparison) (Holder 1993). The project includes community mobilization, encouragement of responsible beverage service by alcohol outlets, a program to reduce underage drinking, increased enforcement of DUI sanctions, and attempts to implement local regulations to reduce alcohol availability. No outcome data are yet available.

Summary

Prevention researchers have used the public health perspective—a model that emphasizes the reciprocal interaction among alcohol, the individual drinker, and the social and physical environment in which drinking occurs—to broaden the concept of alcohol-related problems beyond a focus on the drinker alone and toward a recognition that environment also should be considered in the development of strategies. Within this context, individual-level prevention approaches have multiple goals, including remediating an individual's deficiencies, strengthening competencies, changing beliefs and attitudes about alcohol, or restructuring proximal environments to reduce the risk for alcohol-related problems. Environmental approaches consider the physical and social milieus that regulate exposure to alcohol or mediate the risk that drinking poses to an individual. Recent research illustrates progress in both areas.

Preventing underage drinking and its consequences is a primary concern throughout the alcohol prevention field. Individual-level strategies aimed at this population often are school based because schools offer easy access to the target audience of current and potential young drinkers. Over the last 20 years, scientists have developed a variety of school-based programs, many of which have demonstrated somewhat limited effectiveness. Some recent programs, however, designed and implemented with greater scientific rigor and improved methodologies, have provided promising results. For example, the AMPS program, a resistance education program specifically designed for alcohol prevention, proved to be an effective intervention for alcohol misuse among high-risk sixth grade students. The positive effects of AMPS, which persisted through grade 12, were produced partly by reducing adolescents' vulnerability to peer pressure.

Changing adolescents' normative beliefs about alcohol use also appears to be an important and effective focus for school-based prevention efforts. Students exposed to a normative education curriculum within the Adolescent Prevention Trial had significantly lower alcohol use than those who were exposed to other curricula in the program. The Midwestern Prevention Project provided additional evidence for the effectiveness of normative education. The program, which yielded some declines in the weekly prevalence rates of alcohol use among participating students, achieved most of its effects by altering the perceived peer-group norms about alcohol use (MacKinnon et al. 1991).

Studies indicate that an overwhelming majority of college students, including those under the legal drinking age, have used alcohol. Binge drinking also is a significant problem within this population. An intervention that focuses specifically on risky drinking in college students is the High Risk Drinkers Project. The program uses a "stepped care" model of interventions with freshman participants who are selected on the basis of their reports of risky drinking or alcohol-related problems prior to entering college. Results from a 2-year followup of the program showed that participants had significantly lower levels of drinking and related problems than students assigned to a control group.

Prevention programs employing multilevel communitywide measures are becoming more common as research findings indicate that programs can be more effective when they focus not only on the individual but also on the social and environmental forces that encourage abusive drinking. Individual-level efforts in communitywide programs work synergistically with environmental approaches to reduce or prevent alcohol problems in the target population. One ongoing community program, Project Northland, which includes individual-level interventions (i.e., school-based skills training curricula combined with peer leader, parent, and community support components) applied during the sixth, seventh, and eighth grade years of school, has recently produced some promising findings. Researchers have noted a high level of participation in the program, even among young people whose high-risk status might have lessened their involvement. In addition, the interventions successfully reduced adolescent alcohol use, the tendency to use alcohol, and the combination of cigarette and alcohol use among program participants.

Environmental approaches focus on the physical and social conditions that regulate exposure to alcohol or mediate an individual's risk for drinking. The prevention literature has considered the effect of several relevant issues on levels of consumption and alcohol-related problems, including alcohol availability, alcohol warning efforts, prevention strategies in the workplace and the community, and programs to prevent drinking and driving and violence.

Several studies evaluating the effect of privatization policies on the environmental issue of alcohol availability have demonstrated that alcoholic beverage sales and consumption increase substantially when States enact policy changes that eliminate alcohol retail monopolies and introduce licensed private sales outlets. Privatizing

distribution systems often results in changes in alcohol availability through increased numbers of sales outlets, longer sales hours, and increased promotions and advertising. This information can be useful in forming policy decisions concerning alcohol distribution.

Research continues to show that laws establishing 21 years as the legal minimum drinking age have been effective in reducing youth drinking and related problems, such as traffic crashes, suicides, and pedestrian deaths and other unintentional injuries. Despite these laws, however, most underage youth still drink, thus prompting researchers to explore how underage drinkers obtain alcohol. Various recent studies have shown that underage youth frequently are able to purchase alcohol in a variety of settings without being asked for identification to verify age. Drinking-age laws often are poorly enforced against those who are selling or providing alcohol to underage youth.

Statistics indicate that drinking and driving is a serious public health concern: About 45 percent of all traffic crashes in this country are associated with alcohol use. Designated driver programs, deterrence measures, and lower allowable BACs for young drivers are prevention strategies that have been devised to address this significant problem. In some cases, designated driver programs have produced favorable results. For example, an evaluation of the Wichita Ride Service Program, which provides taxi service to visibly intoxicated patrons from Thanksgiving to January 2, reported that the 123 individuals who used the program in the 1989–1990 season had cars and might have driven themselves if the service had not been available. Thus, the program effectively removed impaired drivers from the road. Another study assessing the designated driver strategy, however, showed that fraternity members who agreed to appoint designated drivers often forgot to do so and when they did remember, the designated drivers typically consumed alcohol, although at less than usual rates. Moreover, although participants had favorable attitudes about the concept, the researchers noted practical problems with the approach that may limit its use.

Another effort used to reduce the incidence of alcohol-related traffic crashes is the establishment of lower allowable BACs for young drivers. The allowable BACs for youth vary by State, ranging from 0.00 to 0.05 percent. An analysis of nighttime fatal crashes in the first four States to implement lower BAC limits revealed a decline of 8 percent attributable to the lower BAC policy. In a subsequent study of 12 States that had implemented lower legal BACs for young drivers before 1991, investigators found that the proportion of fatal single-vehicle nighttime crashes declined 16 percent among young drivers. The investigators also observed that, the lower the allowable BAC, the more profound the effect.

Environmental approaches are important components of communitywide prevention programs. Such programs consider in their development the social, political, and economic factors that collectively can encourage problem drinking. The ongoing Communities Mobilizing for Change on Alcohol Project focuses on changing institutional structures, organizational practices, and public policies to reduce the accessibility of alcohol to youth aged 15 to 20 years. Although effectiveness data are not yet available for the project, baseline data reveal the ubiquity of illegal sales to minors and the ease with which underage youth obtain alcohol. Other communitywide projects that have been evaluated have achieved significant effects on awareness, public support for alcohol prevention, and related attitudes. Many of these studies, however, appear to have effected temporary changes in drinking behavior or the prevalence of alcohol-related problems.

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Chapter 10

Treatment of Alcoholism and Related Problems

Introduction

Across the United States, an estimated 708,255 clients were treated for alcoholism in 10,277 facilities on October 1, 1993, 13.5 percent as inpatients and 86.5 percent as outpatients. Women represented 27.7 percent of the admissions to treatment; whites accounted for 63.7 percent; blacks, 20.0 percent; Hispanics, 11.7 percent; and Asians, American Indians, and other ethnic groups, 3.5 percent. Most clients (72.7 percent) were between 21 and 44 years of age, 6.9 percent were adolescents (under 18 years of age), and 5.0 percent were over 55 years of age.[1] In 1989, the cost of alcoholism treatment delivered in specialized private and public programs was estimated to be $3.8 billion (Dayhoff et al. 1994).

Growing evidence indicates that many people who experience alcohol problems can successfully stop or reduce their alcohol use without participation in formal treatment programs (Sobell et al. 1993; Tucker et al. 1994). Yet people with more severe alcohol dependence or with serious psychiatric or other drug use disorders are likely to participate in specialized alcoholism treatment programs as part of their recovery efforts.

An estimated 9.6 percent of men and 3.2 percent of women in the United States will experience symptoms of alcohol dependence sometime in their lives (Grant 1992). Specialized services for the treatment of alcohol dependence are delivered in two general settings, inpatient and outpatient. Inpatient settings are often used for the early stages of treatment, particularly acute detoxification and short-term residential programs. Outpatient settings provide more long-term, maintenance treatment, with weekly or twice weekly contact for group and individual counseling.

This chapter summarizes recent research across areas central to the treatment of alcoholism. Reviewed first are some diagnostic systems developed to define the disorders of alcohol abuse and dependence for treatment, research, and reimbursement purposes. The newly revised diagnostic criteria for alcohol abuse and dependence and the implications of these diagnostic changes are discussed.

The chapter also addresses recent treatment research on outcomes. Treatment outcome research has traditionally focused on the extent and consequences of alcohol consumption after discharge from treatment as a measure of treatment success or failure. Recent treatment research, however, has incorporated a range of quality-of-life measures, such as restoration of personal relationships and finding and maintaining employment, as additional important indicators of treatment improvement.

Summaries within the chapter of formal and more naturalistic treatment outcome studies highlight significant advances in pharmacotherapy, family and social support therapy, relapse prevention interventions, and behavior-oriented controlled drinking interventions as strategies for change. How client and therapist characteristics independently influence treatment effectiveness is also considered. The research discussed focuses on the impact of patient motivation to change on treatment effectiveness.

Alcohol-dependent persons are at increased risk for other substance abuse and psychiatric disorders. These concurrent problems can complicate alcoholism treatment and decrease overall effectiveness. One area of particular concern is discussed in this chapter: the very high rate of cigarette smoking among patients treated for alcoholism. There has been considerable debate concerning simultaneous treatment for smoking and alcoholism, and research findings are beginning to emerge on this important treatment issue.

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[1] The data are from a special analysis of the 1993 National Drug and Alcoholism Treatment Unit Survey performed by the Substance Abuse and Mental Health Services Administration for this report.

Finally, several recent studies demonstrate robust interaction of specific patient characteristics and types of intervention. As a result of increased concern over cost-effectiveness of services, recent studies have emphasized outpatient care during all phases of recovery. Some models for brief, early intervention as well as those for more structured outpatient detoxification and intensive day-treatment services are presented to show the trends in treatment for alcoholism in the mid-1990s.

Diagnosis of Alcohol Abuse and Dependence

Alcohol dependence is a chronic disorder with a cluster of recognizable symptoms, including physical withdrawal, loss of control over drinking episodes, and continued use of alcohol despite knowledge of having a physical or psychological problem that likely is caused by alcohol (American Psychiatric Association [APA] 1994). The clinical entity alcohol abuse is characterized by a maladaptive pattern of alcohol use manifested by recurrent and adverse consequences associated with drinking, such as failure to fulfill important obligations at work, school, or home; repeated alcohol use in physically dangerous situations; and recurrent legal problems (APA 1994). A person who abuses alcohol may continue to use the drug despite a history of undesirable, persistent, or recurrent social or interpersonal consequences.

In 1994, the APA published the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), which represented the third revision of the diagnostic manual since 1980. Several substantive changes were made in the final DSM-IV criteria for psychoactive substance abuse and dependence as compared with the earlier criteria in the 1987 *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R)(tables 1 and 2). DSM-IV changes included a reduction in the number of symptoms that define alcohol dependence (from nine in DSM-III-R to seven in DSM-IV), an increase in the number of symptoms that define alcohol abuse (from two in DSM-III-R to four in DSM-IV), the addition of a temporal requirement that at least three dependence symptoms co-occur during a 12-month period, the inclusion of criteria for subtyping alcohol dependence on the basis of the presence or absence of the physiologic symptoms of withdrawal and tolerance, and the addition of course descriptors to characterize the recovery status of dependent patients. In a departure from the criteria of DSM-III-R, DSM-IV includes nonoverlapping criteria for dependence and abuse.

Alcohol-dependent patients now can be more precisely characterized by the length of time of abstinence and symptom remission (early remission = longer than 1 month but less than 1 year; sustained remission = 1 year or more). Characterization is also based on whether there is continued presence of one or more abuse or dependence symptoms (partial remission = one or more symptoms present continuously or intermittently during the period of remission; full remission = no symptoms present). The diagnosis also can specify whether the individual has been in a controlled environment in which access to alcohol is restricted.

Two major systems are available for diagnosing alcohol abuse and dependence: the international diagnostic system published by the World Health Organization (WHO), the 10th revision of the *International Classification of Diseases* (ICD-10) (WHO 1992), and the U.S. system published by APA, the DSM-IV (tables 1 and 2). Both classification systems are based on the concept of an alcohol dependence syndrome, in which a cluster of recognizable symptoms (e.g., impaired control, withdrawal, tolerance, and drinking despite problems) co-occurs temporally in the alcohol-dependent patient (Edwards and Gross 1976).

Despite their common theoretical basis, the two diagnostic systems (DSM and ICD) differed significantly in structure and terminology, making comparison of clinical and research findings difficult. Several changes introduced in the DSM-IV criteria increase the comparability of alcohol dependence by the two systems and should facilitate cross-cultural research efforts. Although there is improved agreement in the classification of alcohol dependence, differences persist in the systems for diagnosing the alcohol use disorders of "harmful use" in the ICD-10 and "alcohol abuse" in the DSM-IV (Hasin et al. in press).

In formulating the DSM-IV system, members of the DSM-IV Work Group (APA 1991) agreed that changes in the diagnostic system must be carefully justified. Thus, the researchers explored several issues through field trials to determine the impact of a revised diagnostic system. For example, they considered whether the physiologic symptoms of alcohol withdrawal and tolerance should be required for a diagnosis of alcohol dependence. Based on field trial data, the researchers decided that these symptoms should be used to construct subtypes of alcohol dependence; that is, alcohol dependence with or without physiologic dependence. Researchers also questioned the relevance of the duration criteria used within DSM-III-R. Based on a literature review and consultation with advisors, the DSM-IV Work Group decided to retain within the DSM-IV a duration criterion requiring the co-occurrence of at least three symptoms during a 12-month period. Unlike that of DSM-III-R, the duration criteria of the DSM-IV abuse and dependence categories are qualifiers that are associated with individual diagnostic criteria and not the diagnostic categories. The decision to include duration criteria is consistent with the syndromal formulation of the alcohol dependence syndrome (Grant 1995).

Both the DSM-IV and the ICD-10 have two categories available for diagnosis of alcohol problems: alcohol abuse (or "harmful use" in ICD-10) and alcohol dependence. Symptoms for alcohol dependence, often considered by clinicians as a more severe and pervasive process, are based on the alcohol dependence syndrome described above; all other alcohol-related problems (e.g., social, occupational, legal, or health) are assumed to represent a second, less severe process (Schuckit et al. 1994). Some researchers, however, have questioned the idea that abuse is less severe than dependence. For example, Hasin et al. (in press) noted that if abuse was a milder disorder than dependence, abuse should be the more prevalent diagnosis. According to prevalence estimates, however, dependence is more prevalent than abuse (Grant et al. 1991, 1994).

Furthermore, although the DSM system fundamentally is based on the concept that two distinct processes for alcohol impairment exist, alcohol abuse within the DSM-III-R system was a residual category reserved for people with mild disorders and those at an early stage in a career of alcohol use (Grant et al. 1991). Muthén et al. (1993), however, demonstrated that alcohol dependence and alcohol abuse are distinct disorders, providing evidence that alcohol abuse and dependence do not define opposite ends of a single process in which dependence becomes more severe but rather are distinct phenomena.

Finally, established diagnostic systems have not stipulated specific levels of hazardous alcohol consumption. What is acceptable varies across cultures, time, and individuals as a function of such variables as health, pregnancy, age, and gender. Using a nationally representative sample of U.S. adults, a recent study examined the relationship between alcohol consumption and five DSM-IV symptom domains (Dawson et al. 1995). The results indicated that as alcohol consumption increases, the likelihood of experiencing an alcohol-related problem increases for all five problem domains. This relationship was stronger for the three behavioral domains—impaired control, hazardous drinking, and continued drinking despite problems—than for the two physiologic domains—tolerance and withdrawal. It suggests that the inability of a person to refrain from drinking, despite associated problems, can develop at lower levels of alcohol consumption than are required for the development of tolerance and withdrawal.

Assessment

Patient assessment is usually conducted after admission to treatment, and it is accomplished through the use of diagnostic and clinical interviews and assessment interviews. This ongoing, interactive process provides information that is used to aid in the formal diagnosis of the patient's alcohol problem, characterize the severity of alcoholism and determine the appropriate treatment setting and intensity of treatment, establish treatment goals and strategies appropriate to individual patient needs, and facilitate outcome measurement (Allen 1991).

Assessment Questionnaire Instruments

The success of treatment for alcoholism has been based primarily on the amount and frequency of patients' alcohol use after discharge; secondary outcomes concern the negative consequences of excessive alcohol use (Babor et al. 1994). Instruments developed for these specific outcomes were reviewed in the *Eighth Special Report to the U.S. Congress on Alcohol and Health.*

In the past decade, a dramatic increase in emphasis on quality of life as a critical outcome measure has occurred throughout biomedical research. Recently, this interest has extended into alcoholism research, resulting in the development or adoption of instruments designed to assess different aspects of intrapersonal and person-environment functioning that might be influenced by participation in an alcoholism treatment program (Longabaugh et al. 1994a) (table 3).

Subjective Well-Being/Psychopathology

Earlier studies identified the extent and severity of patient psychopathology as an important predictor of treatment outcome. As a consequence, recent studies have

Table 1. DSM-III-R,* DSM-IV, and ICD-10 diagnostic criteria for alcohol dependence.

DSM-III-R	DSM-IV	ICD-10
	Symptoms	
A. At least three of the following:	A. A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by at least three of the following:	A. At least three of the following exhibited or experienced:
Tolerance		
(1) Marked tolerance—need for markedly increased amounts of alcohol (i.e., at least 50% increase in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of alcohol)	(1a) Need for markedly increased amounts of alcohol to achieve intoxication or desired effect	(1) Increased amounts of alcohol required in order to achieve effects originally produced by lesser amounts
	(1b) Markedly diminished effect with continued use of the same amount of alcohol	
Withdrawal		
(2) Characteristic withdrawal symptoms for alcohol	(2a) Characteristic withdrawal symptoms for alcohol	(2) A physiological withdrawal state
(3) Alcohol often taken to relieve or avoid withdrawal symptoms	(2b) Alcohol taken to relieve or avoid withdrawal symptoms	
Impaired control		
(4) Persistent desire or one or more unsuccessful efforts to cut down or control drinking	(3) Persistent desire or unsuccessful efforts to cut down or control drinking	(3) Difficulties in controlling drinking in terms of onset, termination, or levels of use
(5) Drinking in larger amounts or over a longer period than the person intended	(4) Drinking in larger amounts or over a longer period than the person intended	
Neglect of activities		
(6) Important social, occupational, or recreational activities given up or reduced because of drinking	(5) Important social, occupational, or recreational activities given up or reduced because of drinking	(4a) Progressive neglect of alternative pleasures or interests in favor of drinking
		or
Time spent drinking		
(7) A great deal of time spent in activities necessary to obtain, use, or recover from alcohol	(6) A great deal of time spent in activities necessary to obtain, use, or recover from alcohol	(4b) Increased amount of time necessary to obtain or use alcohol or to recover from its effects

*DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.*
DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*
ICD-10 = *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.*

Table 1. DSM-III-R, DSM-IV, and ICD-10 diagnostic criteria for alcohol dependence *(continued)*.

DSM-III-R	DSM-IV	ICD-10
	Symptoms	
Inability to fulfill roles		
(8) Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home		
or		
Hazardous use		
Use when drinking is physically hazardous		
Drinking despite problems		
(9) Continued drinking despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by alcohol use	(7) Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is caused or exacerbated by alcohol use	(5) Persisting with drinking despite clear evidence and knowledge of overtly harmful physical or psychological consequences
Compulsion		
		(6) A strong desire or sense of compulsion to drink
	Duration Criterion	
B. Symptoms of the disturbance have persisted for at least 1 month or have occurred repeatedly over a longer period of time	B. Symptoms have occurred at any time in the same 12-month period	B. Symptoms have been experienced or exhibited at some time during the prior year
	Criterion for Subtyping Dependence	
	With physiological dependence: evidence of tolerance or withdrawal Without physiological dependence: no evidence of tolerance or withdrawal	
	Course Specifiers	
	Early full remission Early partial remission Sustained full remission Sustained partial remission on agonist therapy in a controlled environment	

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Table 2. DSM-III-R* and DSM-IV diagnostic criteria for alcohol abuse and ICD-10 criteria for harmful use.

DSM-III-R	DSM-IV	ICD-10
	Symptoms	
A. A maladaptive pattern of alcohol use indicated by at least one of the following:	A. A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one (or more) of the following:	A. A pattern of alcohol use that is causing physical or mental damage to health. The diagnosis requires that actual damage has been caused to the physical or mental health of the user
(1) Continued drinking despite knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by alcohol use	(1) Continued drinking despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol	
(2) Recurrent drinking in situations in which it is physically hazardous	(2) Recurrent drinking in situations in which it is physically hazardous	
	(3) Recurrent drinking resulting in failure to fulfill major role obligations at work, school, or home	
	(4) Recurrent substance-related legal problems	
	Duration Criterion	
B. Some symptoms of the disturbance have persisted for at least 1 month or have occurred repeatedly over a longer period of time	B. At least one of the symptoms has occurred within a 12-month period	
	Exclusionary Criterion Related to Alcohol Dependence	
C. Never met criteria for alcohol dependence	C. Never met criteria for alcohol dependence	C. No current diagnosis for alcohol dependence

*DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.*
DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*
ICD-10 = *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.*
Sources: American Psychiatric Association 1987, 1994. World Health Organization 1992. Reprinted by permission.

increased the emphasis on assessment across several domains of psychological function. These studies have focused on measures of depression, anxiety, and more global psychological distress, including the Beck Depression Inventory (Beck et al. 1961), the General Health Questionnaire (Dejour 1995), and the Symptom Checklist 90–Revised (Derogatis 1977). One subscale of the Addiction Severity Index assesses overall psychiatric severity, including number of inpatient and outpatient treatment episodes, medication status, and lifetime and current symptomatology (McLellan et al. 1980).

Although the effects of heavy alcohol consumption on cognitive status have been researched extensively, few studies have explored the potential importance of cognitive status as a mediator of treatment response. More recent studies, however, have examined brief cognitive assessment tools, such as the Shipley Institute of Living Scale (Shipley 1940), the Trail Making Test, and the Mini-Mental Status Examination (Folstein et al. 1975) as predictors of treatment outcome.

Table 3. Domains and associated assessment instruments of quality of life.

Domain	**Instrument/Measure**
Intrapersonal	
Subjective Well-Being/Psychopathology	
Distress	Beck Depression Inventory General Health Questionnaire Symptom Checklist 90—Revised
Anger	Spielberger Trait Anger Scale
Psychopathology	Addiction Severity Index
Neuropsychological status	Shipley Institute of Living Scale Trail Making Test Mini-mental Status Examination
Drinking-Related Beliefs	
Motivation to change	URICA SOCRATES Readiness to change
Self-efficacy	Alcohol Abstinence Self-Efficacy Scale Situational Confidence Questionnaire
Alcohol expectancies	Alcohol Expectancy Questionnaire Negative Alcohol Expectancy Questionnaire
Person-Environment Interactions	
Social Functioning	
Social roles	Psychosocial Functioning Inventory
Social investment	Important people and activities
Environmental Supports for Drinking or Abstinence	
Support for drinking/abstinence from the social network	Important people and activities
Support for drinking/abstinence at work	Your workplace
Support from community self-help	Alcoholics Anonymous involvement

Source: An adaptation and modification of Longabaugh et al. 1994*a*. Reprinted with permission from *Journal of Studies on Alcohol*, Supplement No. 12, pp. 119–129, 1994. Copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, Piscataway, NJ 08855.

Drinking-Related Beliefs

There also has been considerable interest in the role of some drinking-related beliefs as mediators and predictors of change during and after treatment. Patient readiness to change has been examined across different addictive disorders, including smoking, alcoholism, and obesity (see section on patient characteristics in this chapter), and several instruments have been developed specifically to assess this belief.

The University of Rhode Island Change Assessment Scale (URICA) (see table 3) is a 32-item scale designed to measure the stages of change across diverse problem behaviors (Prochaska and DiClemente 1992). URICA score profiles have been used to predict treatment response in research on addictive behaviors such as smoking. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 1995*a*) specifically measures readiness to change alcohol use and related behaviors. The Readiness to Change Questionnaire (Rollnick et al. 1992), which is a very short 12-item instrument developed for use in brief interventions with medical patients, is reported to predict reductions in alcohol consumption 6 months after hospital discharge (Heather et al. 1993).

Another drinking-related belief is self-efficacy; that is, a person's assessment of his or her own ability to carry out a given behavior. In alcoholism treatment research, self-efficacy has been hypothesized to be an important measure of within-treatment change and a predictor of posttreatment outcome. Two instruments have been designed to assess alcohol-related self-efficacy. One is the Alcohol Abstinence Self-Efficacy Scale (DiClemente et al. 1994), a reliable and valid self-report measure that assesses temptation to drink and confidence to abstain in 20 situations with high risk for relapse. The other is the Situational Confidence Questionnaire (Annis and Graham 1988), which measures perceived risk and confidence to resist the urge to drink heavily across a variety of situations. These instruments enable treatment personnel and researchers to match treatment goals (e.g., abstinence or controlled drinking) to self-efficacy measures.

An important set of alcohol-related beliefs are the expectancies that people have concerning the effects of alcohol on psychosocial and physical functioning.

An important set of alcohol-related beliefs are the expectancies[2] that people have concerning the effects of alcohol on psychosocial and physical functioning. The Alcohol Expectancy Questionnaire (Brown et al. 1987) examines expected positive changes after alcohol consumption in the areas of physical and social pleasure, sexual enhancement, social assertiveness, relaxation and tension reduction, arousal, and aggression. In contrast, a 60-item self-report instrument recently developed by McMahon and Jones (1993) assesses negative alcohol expectancies, including same-day, next-day, and continued-drinking consequences. It has been suggested that the decision to drink represents a processing of positive and negative expectancies and that these two sets of alcohol expectancies exist as fairly independent belief structures which may be separately influenced by treatment (Jones and McMahon 1994).

Social Functioning and Environmental Supports for Drinking or Abstinence

Social behavior and functioning are believed to be closely tied to alcoholism treatment outcome, particularly for interventions that focus on interpersonal effectiveness. As a result, increased attention has been given to the definition and measurement of social support as it relates to the treatment of alcoholism. Researchers have posited differential roles and importance for alcohol-specific versus global social support and for support that reinforces versus punishes drinking behaviors (Longabaugh et al. 1993; Love et al. 1993).

The Significant-Other Behavior Questionnaire assesses four types of responses that a significant other can direct toward an alcoholic: support drinking, withdraw during drinking, punish drinking, or support sobriety (Love et al. 1993). Separate but parallel questionnaires for completion by the alcoholic and the significant other provide a means of obtaining information on the correspondence of the alcoholic's and the significant other's perceptions of alcohol-specific responses. These perceptions help form a basis for individualized relationship-oriented interventions.

The Important People and Activities Instrument assesses several key aspects of general and alcohol-specific support provided by the significant persons in a patient's social network (Beattie et al. 1993). The instrument identifies the people with whom the patient spends the most time and measures how important these people are to the patient. It also assesses their drinking status and whether they are supportive of the patient's drinking or abstinence (Longabaugh et al. 1994*a*). A similar brief assessment of support for abstinence versus drinking in the workplace has been shown to predict posttreatment alcohol consumption by frequency and amount (Beattie et al. 1992).

Finally, belief and level of participation in Alcoholics Anonymous (AA) are associated with long-term abstinence in patients participating in treatment for alcoholism (Cross et al. 1990; Gilbert et al. 1991). The Alcoholics Anonymous Involvement Questionnaire

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[2] Alcohol expectancies can be characterized as personalized beliefs that can be predictive of an individual's experimentation with and subsequent use of alcohol.

(Tonigan et al. 1996) provides a brief measure of these important aspects of the patients' recovery environment.

Biological Markers

Identifying sensitive and specific biological markers for acute and chronic alcohol consumption has been a concern of scientists and clinicians for many years. Such markers are used to screen for alcohol abuse in medical settings and other high-prevalence environments, provide feedback during brief interventions to reduce drinking by heavy drinkers, and monitor compliance with alcohol abstinence in patients under treatment. To date, most markers—specifically, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and mean corpuscular volume (MCV)—have not demonstrated enough sensitivity and specificity to be adopted for clinical use in screening for alcohol problems. The inaccuracy of these markers generally stems from the ability of some non-alcohol-related diseases to produce changes in the marker that are similar to changes produced by excessive alcohol use. For example, elevated AST, ALT, and GGT levels are associated with liver pathology, although liver pathology is not necessarily alcohol induced (Bell et al. 1993).

> *Recent studies have reported that CDT detection rates range from 26 to 71 percent, comparable to more widely available and less expensive markers such as GGT and MCV.*

In the last several years, considerable interest has been shown in the potential utility of carbohydrate-deficient transferrin (CDT) as a marker for heavy drinking and alcohol abuse. Research findings have confirmed that CDT elevation is highly specific to heavy alcohol consumption, defined as more than 50 grams of alcohol daily for at least 1 week (Bell et al. 1993, 1994; Potter 1994; Stibler 1991). Few other identified disorders can elevate CDT, and they tend to occur in relatively few patients.

Initial optimism concerning the sensitivity of CDT in detecting heavy drinkers in large heterogeneous drinking populations (e.g., hospitalized patients and general health screening participants) has diminished (Allen et al. 1994). Recent studies have reported that CDT detection rates range from 26 to 71 percent, comparable to more widely available and less expensive markers such as GGT and MCV (Bell et al. 1993, 1994; Nilssen et al. 1992; Salmela et al. 1994; Wickramasinghe et al. 1994). A significant concern is that CDT appears to be less sensitive in women than in men (Gronbaek et al. 1995), possibly because in females CDT levels are normally considerably higher than in males (Anton and Bean 1994; Nystrom et al. 1992; Potter 1994). In a recent study of female college students (La Grange et al. 1995), CDT levels were significantly elevated in women with moderate drinking patterns, compared with levels in abstainers and light drinkers; however, CDT levels also were significantly higher in women using oral contraceptives. The sensitivity of CDT as a marker for heavy drinking in younger drinkers also has been questioned (Nystrom et al. 1992). Thus, although CDT is a specific marker for heavy alcohol use in men, it may not be sensitive enough for screening women or heterogeneous populations of drinkers.

Whereas most markers are useful primarily for the detection of prolonged, heavy drinking episodes, recent evidence indicates that urinary 5-hydroxytryptophol (5-HTOL) may be effective as a marker of recent acute drinking. 5-HTOL levels increase as the dose of alcohol increases and remain elevated for at least several hours, possibly 24 hours or longer, after blood alcohol levels reach zero (Voltaire et al. 1992). In another study, alcohol-dependent patients were monitored for drinking episodes during 6 months of outpatient treatment. The findings indicated that 5-HTOL was more sensitive than either self-reports or the detection of alcohol in urine; however, comparison of CDT and 5-HTOL as biomarkers for alcohol was compromised by low levels of alcohol in patients who were not consuming alcohol daily. Because of their different strengths (CDT for validating patients' self-reports of drinking and 5-HTOL for recent intake), the markers appear to have complementary properties in early detection of relapse and treatment monitoring (Carlsson et al. 1993).

Treatment Intervention

Extent of Treatment Services

In the substance abuse treatment field, the range and intensity of treatment services offered by programs have emerged as important predictors of within-treatment and posttreatment outcomes (McLellan et al. 1993*a*). In one study, McLellan et al. (1993*b*) compared the range and intensity of service delivery and associated outcomes in two inpatient and two outpatient private substance abuse treatment programs for alcohol- or cocaine-dependent employed patients. Overall, the two inpatient programs provided significantly more total services than the outpatient programs did; the increases were primarily in the areas of alcohol and other drug counseling and medical services. Differences in service range and intensity also were observed between the two programs within the same treatment setting. Generally, alcohol and drug use showed comparable improvement in both inpatient and outpatient treatment settings. In other areas of patient functioning (i.e., health, employment, family, and psychiatric), patients who were treated in programs with services that met their particular areas of need showed the greatest improvement in those areas after discharge. These findings suggest the importance of incorporating a range of services within treatment facilities to meet the diverse psychosocial needs of alcoholism patients.

Another study by McLellan et al. (1994) analyzed factors affecting the 6-month outcome for 649 male and female cocaine- , opiate- , and alcohol-dependent adults treated in inpatient and outpatient settings, in 22 publicly and privately funded programs. Based on pretreatment interviews using the Addiction Severity Index and during treatment and posttreatment interviews using the Treatment Services Review, the investigators showed that treatment for substance abuse resulted in significant improvement in substance use outcomes. However, it had little effect on psychosocial outcomes. Conversely, even though a range of psychiatric services (e.g., counseling to improve employment and family relations) did not effect significant change in substance abuse, these services were positively predictive of the patients' psychosocial outcomes. This suggests that similar factors are predictive of outcome in a specific area, regardless of the treatment setting.

Brief Interventions

People who are dependent on alcohol have been the focus of most research on alcoholism treatment. However, many persons abuse alcohol without being dependent on it (Grant et al. 1994). Although they probably do not need intense therapy, alcohol abusers might respond favorably to "brief intervention," which has been described by WHO (1994) as

> A therapeutic strategy that combines early detection of hazardous or harmful substance use and treatment of those involved. Treatment is offered or provided before such time as patients might present of their own volition, and in many cases before they are aware that their substance use might cause problems. It is directed particularly at individuals who have not developed physical dependence or major psychosocial complications. Early intervention is therefore a proactive approach, which is initiated by the health worker rather than the patient (p. 36).

Brief intervention differs from most other treatments for alcohol problems because (1) it is generally restricted to four or fewer sessions; (2) it is usually performed in a treatment setting not specific for alcoholism, typically a primary health care context; (3) it is commonly performed by personnel who have not specialized in addiction treatment; (4) it is usually provided to individuals at risk for dependence or serious consequences rather than those who could already be diagnosed as alcohol dependent; and (5) its goal may be moderate drinking rather than total abstinence.

Reviewers have categorized brief interventions in two ways: empirically, by the time required for treatment (Babor 1994; Richmond and Anderson 1994*a*), and conceptually, according to the nature or content of the treatment process (Sanchez-Craig and Wilkenson 1992). In the latter approach, brief intervention may be distinguished as (1) *advice*—recommending behavior change, providing health education, and sometimes giving guidelines for "sensible drinking" or (2) *counseling*—advice plus information on how to achieve the goals of the intervention. Advice as brief intervention may be further subdivided as (a) *general*—recommending less drinking and emphasizing risks or (b) *specific*—recommending clear limits on alcohol use. Counseling may be therapist assisted or self-help, involving written materials to be studied by the patient. In recent years, single-session, self-help brief intervention has received the greatest amount of research attention.

Brief intervention is offered for several reasons. First, many people who are not dependent on alcohol nevertheless drink at hazardous levels or appear to be in the early stages of developing problems with alcohol. Second, brief intervention is inexpensive; can readily be incorporated into many settings; and is reasonably effective, at least with nondependent alcohol abusers and individuals whose drinking puts them at risk for developing severe problems. Third, brief intervention in no way precludes subsequent application of more intensive intervention. People who do not respond well can be referred later to more definitive treatment. Those on a waiting list for more intensive treatment might, in the interim, be maintained with brief intervention.

Finally, most research on the effectiveness of brief intervention has excluded alcohol-dependent patients, referring them instead to more intensive treatment. Few statistics are available to show how many referred patients enroll in more intensive intervention programs. In fact, some investigators (e.g., Chafetz 1961; Chafetz et al. 1962; Luckie et al. 1990/1991) have suggested that without special procedures such as followup notes or telephone calls, empathetic discussion, and preparation for participation in more intense treatment, few alcoholics referred from primary care settings actually enter more intensive treatment programs.

> *Although brief intervention has generally been demonstrated to be effective, more research is needed to identify the types of patients best suited to these programs, rather than simply assessing the patient's drinking or response to intensive treatment.*

Studies in many countries have evaluated the effectiveness of brief intervention for alcohol problems. In a thought-provoking meta-analysis, Bien et al. (1993) evaluated the efficacy of brief intervention in 32 of these trials. They evaluated outcomes ("strength of effect") on the basis of preintervention and postintervention comparisons of alcohol behavior variables and contrasts between brief intervention and alternative treatment or no-treatment control conditions. Across studies, the effectiveness of brief intervention was generally quite high (between 0.70 and 0.80), producing an average positive change of about 27 percent. The mean effect of brief intervention versus a no-formal-intervention-control condition was less (0.38), but still meaningful, suggesting that screening itself must be considered in evaluating the effectiveness of brief intervention. In other words, simply asking about their drinking and its consequences may influence some patients to reduce consumption. In the samples studied (mainly early-stage problem drinkers or individuals drinking at excessive levels), brief intervention appeared to be about as effective as more intensive treatment.

Little is known about the patients for whom brief intervention might prove most effective. For example, men and women may be differentially responsive. Anderson and Scott (1992) found that by 12-month followup, heavy-drinking men who received brief intervention achieved greater reduction in weekly alcohol use than heavy-drinking men who only had been screened for alcohol problems. However, for heavy-drinking women, brief intervention was no more beneficial than screening alone (Scott and Anderson 1991). A multinational study by Babor and Grant (1992) revealed a similar gender effect, corroborating earlier reports from Robertson et al. (1986) and Elvy et al. (1988) that the effects of brief intervention differed between men and women.

Motivation has been studied with regard to its contribution to the effectiveness of brief intervention. Among patients highly motivated to reduce their drinking and confident that they could change on their own, 77 percent decreased their drinking when given a self-help manual with specific instructions; only 28 percent of such patients reduced their drinking when given materials containing only general advice (Spivak et al. 1994). However, Heather et al. (1993) found motivational interviewing more effective than skill-based counseling for patients low in initial motivation to change. Although brief intervention has generally been demonstrated to be effective, more research is needed to identify the types of patients best suited to these programs, rather than simply assessing the patient's drinking or response to intensive treatment.

In an effort to identify specific features of brief intervention that are associated with effectiveness, Miller and Sanchez (1994) posited six "active ingredients," elements referred to by the mnemonic term "FRAMES":

- **F**eedback on personal risk for alcohol abuse or excessive consumption
- **R**esponsibility of the patient for changing drinking behavior
- **A**dvice to the patient to diminish or cease consumption
- **M**enu of ways to reduce drinking
- **E**mpathetic rather than confrontational counseling style
- **S**elf-efficacy or optimism of the patient concerning ability to make changes

It is unclear whether providing patients with alternatives for reducing their drinking, as suggested by the menu element, is an effective strategy. It may be that alternatives enhance a patient's motivation; effectiveness may also result from a patient's personal knowledge that has important implications for optimal treatment.

The meta-analysis by Bien et al. (1993) supports the credibility of the FRAMES concept, suggesting that the efficacy of brief intervention in the trials varied as a function of the extent to which these elements were incorporated. A study by Miller and Rollnick (1991) demonstrated the importance of one FRAMES element. The investigators noted that an empathetic counseling style was associated with a drinking reduction of 77 percent versus a reduction of 55 percent achieved using a confrontational mode of counseling. Other factors that may contribute to the effectiveness of brief intervention include timing, tailoring the intervention to the patient's readiness to change, assessment process as well as followup reviews of patient progress, interpersonal influence exerted by the health care practitioner, and support for the patient's improvement from his or her living environment.

Ongoing research indicates the potential deleterious effects of repeated, unmedicated alcohol withdrawal episodes for increasing seizure risk during detoxification of alcohol-dependent patients.

Unfortunately, an array of practical barriers impede the routine implementation of brief intervention in primary health care settings (e.g., Babor et al. 1986; Richmond and Anderson 1994*b*), such as general practitioners' resistance to engage in preventive activities, inattention to screening for possible alcohol problems, lack of confidence concerning how to intervene once cases have been identified, concern that raising the issue of alcohol use may offend patients, and doubts that the intervention will be successful. Furthermore, training in the skills required to screen for alcohol problems and to intervene is typically not included in professional education curricula, although some programs have recently been developed (e.g., College of Family Physicians of Canada 1993; NIAAA 1995*b*).

Finally, there is an economic barrier to brief intervention. Systems for reimbursement of health workers and institutions, whether privately or publicly funded, often do not provide incentives for brief interventions.

Pharmacotherapy

Research is rapidly advancing knowledge of the neurobiological mechanisms underlying the effects of alcohol. Such knowledge is proving to be useful in efforts to develop pharmacotherapies for alcoholism using various classes of drugs that affect different neurotransmitter systems, including the dopamine, serotonin, and opioid receptor systems. Recent studies have placed increased emphasis on patient-treatment matching to identify subgroups of patients who may be particularly responsive to different classes of drugs. Across drug classes, improved strategies are needed to enhance medication compliance as a means to improve treatment outcome.

Detoxification Agents

Ongoing research indicates the potential deleterious effects of repeated, unmedicated alcohol withdrawal episodes for increasing seizure risk during detoxification of alcohol-dependent patients (Lechtenberg and Worner 1991). In light of this "kindling" effect, there is continued interest in the development of optimal pharmacotherapeutic protocols for alcohol withdrawal treatment. Optimal agents should have rapid onset of therapeutic effects, antiepileptic properties, low potential for accumulation in the body that can lead to excessive sedation, and availability of a drug antagonist[3] to reverse severe side effects that might develop (Pycha et al. 1993).

Historically, benzodiazepines have been most widely used for the management of alcohol withdrawal, and research continues on this drug group. For example, Pycha et al. (1993) recently showed that continuous intravenous infusion of the benzodiazepine flunitrazepam provides effective management of withdrawal delirium in medically compromised patients. Vegetative and psychopathological symptoms (e.g., tremor, sweating, hallucinations, motor agitation, and confusion) remitted rapidly. The researchers observed no evidence of seizure activity during or after drug treatment.

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[3] An antagonist is an agent that blocks or reverses actions or effects of another agent.

The utility of a newer benzodiazepine, alprazolam, for alcohol withdrawal management is also of interest because it decreases the cardiovascular hyperactivity associated with alcohol withdrawal. In a double-blind study of alcohol-dependent patients with moderate withdrawal symptoms and no history of withdrawal seizures or other medical complications (Adinoff 1994), alprazolam decreased withdrawal symptoms more effectively than clonidine or placebo. There also was tentative evidence of increased effectiveness of alprazolam as compared with diazepam, a benzodiazepine widely used for withdrawal management, although these effects did not achieve statistical significance, possibly due to the small sample size.

Another recent randomized, double-blind, controlled trial demonstrated the beneficial effects of administering pharmacologic treatment for control of withdrawal symptoms on an "as-needed" basis. Detoxification unit inpatients required lower doses of chlordiazepoxide and less time in treatment (100 vs. 425 mg of the drug and 9 vs. 68 hr, respectively) than patients who received medication on a standard, fixed-schedule therapy. Neither the severity of withdrawal nor the incidence of seizures and delirium tremens differed between individuals on the symptom-triggered therapy and those receiving the benzodiazepine four times daily (Saitz et al. 1994).

In December 1994, naltrexone (ReVia®) was approved by the U.S. Food and Drug Administration for the treatment of alcoholism.

Finally, because of the potential abuse liability and sedative effects of the benzodiazepines, efforts continue to identify effective withdrawal medications from other classes of drugs. A recent well-controlled evaluation of carbamazepine (Stuppaeck et al. 1992) revealed that it tended to be more effective than the benzodiazepine oxazepam in reducing withdrawal symptoms. Carbamazepine offers several potential advantages for withdrawal treatment: relatively low abuse liability, reduced sedation, and antikindling effects for amelioration of future seizure activity (Gallant 1992).

Alcohol-Sensitizing Agents

Recent research on the alcohol-sensitizing agents disulfiram and calcium carbamide (not available in the United States) has focused primarily on strategies for enhanced compliance with the prescribed medication regimen (Brewer 1993). In a comprehensive review of techniques to improve patient compliance, Allen and Litten (1992) concluded that, in general, patient incentives, treatment contracts, and medication instructions have improved the consistency of disulfiram use and reduced alcohol consumption, at least during the medication period.

One recent study compared patient compliance with a calcium carbamide regimen under standard conditions of physician advice for medical management of the drinking problem and patient compliance under a relapse prevention protocol to promote increased self-efficacy (Annis and Peachey 1992). Relapse prevention counseling included instruction on the use of medication during high-risk drinking situations and explicit guidelines for decreasing reliance on medication over time. Patients in the relapse prevention group took more medication during the 4-month active treatment and 6-month followup periods. Patients in both groups showed comparable, marked improvement on alcohol consumption measures during treatment; however, patients in the relapse prevention group showed superior maintenance of drinking reductions 18 months after treatment. These findings suggest that psychosocial treatment that provides specific supportive strategies for use of medication and decreasing reliance on medication may enhance compliance and improve long-term treatment gains.

Of continuing interest as an alternative to psychosocial treatment interventions is the development of long-acting, sustained-release medication preparations that would reduce the demands for patient compliance. Disulfiram implants generally have not been clinically effective because of inadequate drug release and the high risk for infection and other adverse reactions at the implant site (Liskow and Goodwin 1987; Wilson et al. 1984). Alternative disulfiram preparations, including aqueous suspensions (Phillips and Greenberg 1992) and micropellets (Cid et al. 1991) under development, appear to offer increased bioavailability and reduced adverse side effects.

Anticraving Agents

In December 1994, naltrexone (ReVia®) was approved by the U.S. Food and Drug Administration for the treatment of alcoholism. This was the first approval of a drug for the treatment of alcoholism in the nearly 50 years since disulfiram (Antabuse) was approved in 1948.

Two 12-week, double-blind clinical trials (O'Malley et al. 1992; Volpicelli et al. 1992) provided evidence of the effectiveness of naltrexone in decreasing alcohol craving and drinking days among patients participating in psychosocial treatment. Naltrexone prevented relapse to heavy drinking (consumption of five or more drinks per occasion) among those patients who resumed drinking. Among placebo-treated patients, the risk for relapse was more than twice that of naltrexone-treated patients.

Similar findings have come from a pilot study of nalmefene, a new long-acting, orally active opiate antagonist (Mason et al. 1994). Nalmefene offers the potential clinical advantage of no dose-dependent liver toxicity as well as more sustained and universal opiate antagonist effects (i.e., effects at the mu, kappa, and delta opiate receptors, compared with naltrexone's primarily mu-receptor blockade). Subjects receiving a moderate dose of nalmefene reported significantly lower relapse rates and fewer drinks per drinking day than subjects receiving placebo.

In the late 1980s, a series of studies suggested that agents that increase the synaptic availability of serotonin may produce modest decreases (15 to 20 percent) in alcohol consumption of heavy drinkers (Naranjo et al. 1987, 1990). The subjects in those studies were recruited for participation through advertisements. This research was recently expanded to include alcohol-dependent patients but has yielded mixed results. Gorelick and Paredes (1992) reported that the serotonin uptake inhibitor fluoxetine produced a modest 14-percent reduction in alcohol consumption during the first week of a 4-week study of alcohol-dependent, treatment-seeking male patients who had regular access to alcohol on a research ward.

> *Expectancies about the long-term rather than same-day or next-day negative consequences of drinking appeared to be the most highly predictive of drinking outcomes.*

In a more recent 6-week clinical trial of alcohol-dependent, treatment-seeking male patients, Sellers et al. (1994) found no overall difference between placebo and low and high doses of ondansetron (a serotonin antagonist) on any alcohol consumption measure. Subjects classified on the basis of their baseline drinking behavior as moderate and heavy drinkers (consuming up to 10 or more than 10 standard drinks per drinking day, respectively) received low or high doses of ondansetron. Among moderate drinkers, those receiving a low dose of the drug had a significant reduction in drinking, relative to those receiving the high dose or placebo. No drinking differences were observed across dose conditions for heavy drinkers.

This apparently selective effectiveness with moderate but not heavy drinkers was also reported for a 5-week clinical trial of the serotonin reuptake inhibitor citalopram (Balldin et al. 1994). However, a more recent study of the effectiveness of citalopram did not replicate this finding (Naranjo et al. 1995). Thus, the utility of these agents may be primarily with moderate drinkers rather than with patients who have more severe alcohol dependence.

Relapse Prevention Interventions

Role of Alcohol-Related Beliefs in Relapse

People's expectancies about the effects of alcohol are believed to play an important role in their decisions to start and maintain drinking (see Chapter 2, Genetic, Psychological, and Sociocultural Influences on Alcohol Use and Abuse, and Chapter 9, Prevention of Alcohol Problems; also see discussion of expectancy theory in the *Eighth Special Report to the U.S. Congress on Alcohol and Health*). Such expectancies are believed to be central in relapse occasions after treatment (Brown 1985). In an outpatient study of drinking moderation by problem drinkers, decreases in positive alcohol expectancies were associated with decreased heavy drinking posttreatment (Connors et al. 1993). Changes in alcohol expectancies were not apparent immediately after treatment but emerged over the 18-month followup period, making it unclear whether expectancies affected drinking behavior or decreased drinking affected expectancies.

In related work, Jones and McMahon (1994) found that higher levels of negative alcohol expectancies were associated with higher abstinence rates after residential treatment. Expectancies about the long-term rather than same-day or next-day negative consequences of drinking appeared to be the most highly predictive of drinking outcomes. These studies suggest that drinking decisions after treatment are influenced by both positive and negative alcohol expectancies and that both should be actively addressed during treatment interventions.

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Self-efficacy also has been shown to predict the treatment outcome of alcoholism patients. In earlier research, self-efficacy has been found to increase as a function of participation in treatment and to be associated with improved drinking status after discharge from treatment (Burling et al. 1989; Solomon and Annis 1990). It is hypothesized that patients who are high in self-efficacy are more likely to use active coping skills and therefore are more likely to avoid relapse to substance use.

Two recent studies have demonstrated an interaction of self-efficacy and aftercare participation following initial intensive therapy. Rychtarik et al. (1992) found that patients who were high in self-efficacy and also had high levels of aftercare participation experienced significantly better drinking outcomes than all other patient groups. In contrast, patients with low self-efficacy and low levels of aftercare participation had significantly worse outcomes than all other patient groups. Most important, aftercare participation improved treatment outcomes for those patients who were initially low in self-efficacy.

Alcohol-related problems with interpersonal relationships significantly increase the likelihood of seeking treatment in alcoholism programs compared with achieving sobriety without formal assistance.

Similar results were obtained in a randomized clinical trial of aftercare participation following behavioral marital therapy (McKay et al. 1993). In the no-aftercare condition, patients with low as compared with high self-efficacy had lower abstinence rates and more heavy-drinking days during 1-year followup. In the aftercare condition, patients who initially reported low self-efficacy improved in self-efficacy and drinking outcomes during aftercare treatment, whereas aftercare treatment was observed to have little effect for patients with high initial self-efficacy. These studies suggest that post-treatment aftercare may be particularly important for those patients who report low self-efficacy and may contribute to overall improvement in treatment effectiveness.

Coping Skills Interventions

Measurement of relapse-relevant coping skills in alcoholism treatment patients has proved to be methodologically problematic because most measures assess general rather than alcohol-specific skills. In response to these problems, Monti et al. (1993) have developed an alcohol-specific role-play assessment instrument that provides behavioral, cognitive, and affective measures associated with actual coping performance in simulated high-risk situations. Self-report measures of urge, anxiety, and difficulty in the situation were strongly associated with coping performance during the role-play activities, and earlier research found that self-report measures significantly improved during cognitive behavior mood-management and communication skills training (Monti et al. 1990). In addition, role-play responses at the end of treatment were predictive of drinking outcomes 6 months after treatment.

In a randomized clinical trial of interactional therapy and coping skills training, clients in both groups demonstrated improvements in self-reported urge to drink during role-play assessments from pretreatment to posttreatment; these improvements were associated with overall improvements in drinking status after treatment (Kadden et al. 1992). When specific treatment conditions were examined, pretreatment role-play measures of skill, anxiety, and urge to drink interacted with type of treatment to determine outcomes. Patients who did poorly in the role plays experienced better outcomes when given coping skills training, whereas patients who did well in the role plays had better outcomes after interactional therapy. These findings suggest that targeted treatment can improve drinking outcomes among patients with specific deficits in alcohol-related coping skills.

Social and Family Interventions

Alcohol-related problems with interpersonal relationships significantly increase the likelihood of seeking treatment in alcoholism programs compared with achieving sobriety without formal assistance (Tucker and Gladsojo 1993). Given the importance of relationship problems in prompting entry into treatment, research generally has confirmed the importance of family and social support and of interventions targeting relationship enhancement in alcoholics' short-term and long-term recoveries (Atkinson et al. 1993). The findings of a recent study of long-term outcomes of socially stable patients after residential treatment (Finney and Moos 1992) suggested that the availability of posttreatment social resources was associated with increased rates of remission and decreased mortality at 10-year followup.

On the basis of evidence favoring the role of social support in sobriety, interventions have been developed to improve the quality of interpersonal relationships and to teach alcohol-relevant communication and problem-solving skills to patients in alcoholism treatment and their spouses. Earlier studies showed that behavioral marital therapy was more effective than either individual counseling or interactional couples therapy, although the differential effectiveness of the marital therapy declined during the 2-year followup interval (O'Farrell et al. 1992). Researchers later examined the relative effectiveness of behavioral marital therapy with and without extended couples' relapse prevention aftercare for male alcoholic patients and their wives (O'Farrell et al. 1993). Over a 1-year followup period, alcoholics who received relapse prevention aftercare had experienced improved drinking and marital outcomes and showed greater use of specific therapeutic behaviors targeted by behavioral marital therapy.

Research also has begun to focus on patient and environmental factors that may predict which patients respond most successfully to relationship enhancement interventions. Longabaugh et al. (1993) examined the effects of patients' social investment (defined as a person's dependence on other people for rewards) on their response to social support for alcohol abstinence and their actual posttreatment alcohol use behaviors. The results of randomly assigning patients to either individually focused cognitive behavioral therapy or relationship enhancement treatment demonstrated that patients who were high social investors experienced more days of abstinence from alcohol when posttreatment social support was high rather than low. In contrast, the level of posttreatment social support had little influence on alcohol abstinence in patients who were low social investors. Furthermore, the investigators observed an interaction between the type of treatment and patients' levels of social support. Patients with low social support improved most in individually focused cognitive behavioral therapy and least in relationship enhancement therapy, whereas patients who had high posttreatment social support did equally well in both treatments. These findings suggest that relationship therapy may not be indicated for patients whose social support systems have been severely compromised by their drinking but that it can be successfully targeted to those patients who are both highly invested in their social relationships and most likely to experience high levels of social support after treatment.

Controlled Drinking Interventions

The appropriateness of controlled drinking as a therapeutic goal for alcoholism treatment patients remains highly controversial in the United States. Various patient characteristics influence whether controlled drinking is appropriate, including severity of dependence, extent of drinking history, psychological dependence, prior treatment episodes, and current liver damage.

Various patient characteristics influence whether controlled drinking is appropriate, including severity of dependence, extent of drinking history, psychological dependence, prior treatment episodes, and current liver damage.

In a recent survey of approximately 200 randomly selected U.S. treatment programs (Rosenberg and Davis 1994), more than three-quarters of the responding treatment providers found controlled drinking unacceptable as a treatment goal. This position was almost universal among respondents representing residential programs, but only about one-half of those representing outpatient alcoholism programs found controlled drinking to be an unacceptable treatment goal. Among respondents who accepted controlled drinking as a therapeutic goal, the majority advocated it for fewer than one-quarter of their treatment patients. Respondents cited acceptance of the disease model of alcoholism and use of AA as a treatment intervention as the bases for their rejection of controlled drinking. In general, program respondents indicated an unwillingness to negotiate treatment goals with their clients. These findings for U.S. treatment programs stand in contrast to the much higher levels of acceptance of controlled drinking among British treatment providers. Approximately 75 percent of program respondents from the United Kingdom accepted controlled drinking, although (as in the United States) they recommended it for fewer than 25 percent of the patients in their programs (Rosenberg et al. 1992).

Treatment outcome studies continue to demonstrate successful maintenance of controlled drinking by a small subset of treated patients. Miller et al. (1992) examined outcomes at 3.5, 5, 7, and 8 years for four cohorts of problem drinkers[4] (90 percent self-referred in response to media announcements, 10 percent referred by courts and other agencies) who were treated with either moderation-oriented or abstinence-oriented behavioral self-control training. Long-term outcomes for the 99 subjects were 23 percent abstinent, 14 percent asymptomatic, 22 percent improved but impaired, 36 percent unremitted, and 5 percent deceased. At the time of treatment intake, most abstainers had self-selected abstinence as their treatment goal, whereas asymptomatic drinkers had almost universally adopted moderation as a goal. Long-term followup indicated that patients' status as abstinent or unremitted during the first posttreatment year was highly associated with comparable status at long-term followup. In contrast, the presence of controlled drinking during the first year of followup did not reliably predict long-term sustained asymptomatic alcohol use. Patients demonstrating controlled drinking during this period had similar probabilities of sustained improvement or deterioration. In general, high initial levels of alcohol dependence and a positive family history of alcoholism were poor prognostic indicators for long-term asymptomatic drinking. In contrast, those patients who rejected the label of alcoholic and the goal of abstinence at treatment intake were most likely to be successful in achieving stable asymptomatic drinking through extended followup, suggesting the importance of attending to patients' self-assessments and treatment goals.

> *Based on a survey of a representative sample of U.S. adults, an estimated 9 percent have attended an AA meeting at some time in their lives, and 3.6 percent have attended an AA meeting within the last year.*

In a more recent study of behaviorally oriented residential treatment in a British program that explicitly accepted the goal of controlled drinking (Booth et al. 1992*a,b*), 64 percent of patients selected an abstinence goal. At 1-year followup, 27 percent of patients had successful outcomes, 35 percent had equivocal outcomes (more than 6 months abstinent or drinking within acceptable limits and no rehospitalization), and 38 percent were treatment failures. Adoption of abstinence or controlled drinking as the treatment goal did not influence outcome at followup. Patients who were previously treated for alcohol problems or showed liver damage at admission to treatment were most likely to experience poor outcomes. Frequency of outpatient aftercare, but not length of stay in residential treatment, was strongly associated with improved outcome after 1 year. Overall, the controlled drinking literature has demonstrated that drinking moderation can be an appropriate therapeutic goal for a select group of alcoholism treatment patients, particularly those with less severe dependence symptoms and those who reject traditional abstinence-oriented labeling and goal setting

Alcoholics Anonymous

As AA and other 12-step programs continue to grow, so has research interest in the impact and potential mechanisms of change of this self-help approach. Based on a survey of a representative sample of U.S. adults (Room and Greenfield 1993), an estimated 9 percent have attended an AA meeting at some time in their lives, and 3.6 percent have attended an AA meeting within the last year. Approximately one-third of respondents indicated they attended meetings for help with their own drinking problems. Additional survey findings indicated that AA attendance was considerably more likely than attendance at any other support or therapy group when help was sought for one's own drinking problem; more than twice as many people attend AA as all other 12-step programs.

An examination of the rates of attrition among AA members by using anniversary announcements published in the Finnish AA newsletter (Mäkelä 1994) found that the annual rates of attrition decreased with increased length of sobriety. Retention rates were 67 percent for members with 1 year of sobriety, 85 percent for those with 2 to 5 years of sobriety, and more than 90 percent for those with more than 5 years of sobriety. No gender differences were observed in AA attrition. Overall, approximately 90 percent of all AA members with at least 1 year of sobriety continued in the fellowship for another year.

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[4] The researchers determined that alcohol abuse was diagnosable in all cases, and a history of alcohol dependence was present in 52 percent of the cases.

In addition to more precise estimates of membership levels and retention, research efforts have been directed toward characterizing the active mechanisms of change involved in AA participation. Montgomery et al. (1993) examined key characteristics of the group process across four established AA meetings. On the basis of members' ratings, all four meetings were comparable in promoting spirituality and discouraging innovation. However, two out of the four meetings were rated as lower in cohesion and higher in aggression; these same meetings tended to be rated as less structured. Of considerable interest would be research to examine the impact of differences in meeting dynamics on attrition and drinking outcomes.

Finally, Snow et al. (1994) examined the relationship between AA attendance and affiliation and the use of a variety of cognitive and behavioral change processes. In general, individuals who had higher levels of AA involvement reported greater use of behavioral change mechanisms, including stimulus control, behavioral management, and use of helping relationships. This study represents an important initial effort to define the "active ingredients" of sobriety maintenance associated with AA affiliation. These findings await replication and extension in future studies.

Nontreatment Factors Related to Outcome

Patient Characteristics

For decades, research has sought to identify patient characteristics that accurately predict treatment outcome. The ability to forecast reliably which patients will be successful or unsuccessful in a particular treatment modality could provide some scientific and therapeutic advantages, including a rapid intervention to "jump start" the treatment episode and prevent treatment dropout; more intensive treatment services that could be used during the early phases of treatment and gradually phased out once the patient's condition has successfully stabilized; and an alternative treatment strategy for successfully matching patients to more appropriate therapeutic services. Historically, studies have focused on demographic or personality characteristics of patients; however, more recently, the focus has shifted to biological, social, and environmental characteristics that may be more amenable to change through treatment interventions.

Studies have identified biological variables that correlate with posttreatment relapse in alcohol-dependent patients. Alcohol stimulation of dopamine receptors in the brain is believed to be associated with the reinforcing effects of alcohol during alcohol consumption (see Chapter 3, Actions of Alcohol on the Brain). Recently, levels of growth hormone secretion before detoxification were studied in alcoholics as an indirect measure of brain dopamine receptor activity (Heinz et al. 1995). Results showed that these levels (and presumably dopamine receptor sensitivity) were significantly decreased in alcoholics who relapsed shortly after treatment, compared with levels in patients remaining abstinent. These findings suggest that reduced dopamine receptor sensitivity may be related to the development of dysphoria and alcohol craving, which in turn increase the risk for relapse in recently detoxified alcoholics.

Two other studies examined the relationship between cognitive/information-processing measures obtained shortly after drinking cessation and subsequent posttreatment relapse. Glenn et al. (1993) measured event-related brain potentials (ERPs) in alcoholic inpatients who had been sober for 3 to 6 weeks and then monitored their alcohol use over the next 13 months. ERPs of alcoholics who subsequently relapsed indicated more information-processing deficits than ERPs of alcoholics who remained abstinent. Similarly, the electroencephalographic and autonomic activities of alcohol-dependent patients measured 7 to 10 days after drinking cessation were significantly different for subjects who subsequently relapsed to alcohol use within the next 3 months (Bauer 1994). These findings are suggestive of the potential role of biological, and particularly cognitive or information-processing, factors in relapse to alcohol. However, it is not clear whether such biological variables are traits that predate the onset of the alcohol use disorder or the consequences of more severe alcohol problems or other associated factors. For example, the severity of alcoholism (measured by length of heavy drinking, amount of daily alcohol consumption, and number of previous treatment episodes) has been found to predict relapse and readmission to treatment among alcoholic inpatients (Moos et al. 1991; Yates et al. 1993).

In recent years, increased attention has been paid to the role of interpersonal variables and particularly social support for the maintenance of sobriety in alcoholism treatment patients. Examining the roles of social support for alcohol involvement and for general subjective well-being in alcoholism treatment outcomes, Beattie et al. (1993) have divided their attention between the relationships in the workplace and general affiliative relationships. Their findings indicate that general affiliative support and workplace social support are strongly associated with patients' self-reports of subjective well-being, whereas alcohol-specific workplace support and affiliative support are related to the extent of patients' alcohol involvement. The authors identified no direct causal relationship between patients' level of alcohol involvement and subjective well-being.

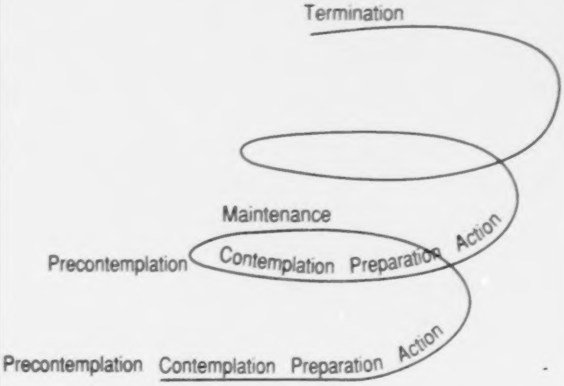
A 4-year followup study of late-life problem drinkers yielded similar findings concerning the importance of alcohol-specific support from one's spouse and friends on the stability of abstinence (Schutte et al. 1994). These findings on the role of social support in treatment outcome highlight the potential importance of involving family and friends in the treatment process. They also show the potential utility of targeting specific aspects of social relationships for intervention.

Finally, there has been growing interest in the predictive utility of patients' readiness to change dysfunctional behaviors as a predictor of treatment outcome. An example of a promising way to look at patient motivation is the "stages of change" model (Prochaska et al. 1992*a*), which defines five stages:

- Precontemplation, in which the individual is generally unaware of the problem and has no intention of changing in the near future
- Contemplation, in which the individual is aware of the problem and thinking about change but has not made a serious commitment to change
- Preparation, in which the individual may have made small inroads into the behavior change but has not reached a level of effective action
- Action, in which the individual modifies behavior, experiences, or environment to overcome the behavior
- Maintenance, which focuses on relapse prevention and consolidation of the accomplishments of the action phase

Under this model (illustrated in figure 1), progress is not linear but cyclical, with individuals making gains, relapsing (although not slipping back to the initial stage), then moving forward again with new strategies based on the prior mistakes.

Figure 1. A spiral model of the stages of change.



Source: Prochaska et al. 1992*b*. In search of how people change: Applications to addictive behaviors. *American Psychologist* 47(9): 1102–1114, 1992. Copyright © 1992 by the American Psychological Association. Reprinted with permission.

In one study of patients receiving outpatient alcoholism treatment (DiClemente and Hughes 1990), patient groups with different stages of change profiles reported different reasons for drinking, concerns over the consequences of drinking, and levels of temptation and self-efficacy to stop drinking that corresponded with their identified stages of behavior change. For example, the "contemplation" and "action" groups reported significantly greater problems associated with their alcohol use than the "precontemplation" group, although self-reported drinking levels and withdrawal symptoms were comparable across groups. Research on smokers shows that treatment progress has a strong correlation with the pretreatment stage of change (Prochaska et al. 1992).

The stages of change model is being applied to such diverse behaviors as smoking, alcohol and other drug abuse, condom use for AIDS (acquired immunodeficiency syndrome) prevention, sunscreen use, weight control, and exercise habits. It may be a promising approach to patient-treatment matching based on readiness for treatment (Prochaska et al. 1992*b*).

Treatment Counselor Characteristics

Treatment counselor style can exert a substantial influence on treatment outcome (Crits-Christoph et al. 1990; Najavits and Weiss 1994), yet there continues to be a paucity of research directed at this important determinant of treatment outcomes. Psychotherapy and substance abuse studies have shown that treatment counselors vary widely in their effectiveness. For example, across some substance abuse treatment studies, different treatment counselors have been shown to have as much as a threefold difference in client retention and treatment effectiveness (Najavits and Weiss 1994). On occasion, such counselor effects have been stronger than the effects of the specific psychotherapeutic interventions under investigation (Crits-Christoph et al. 1991).

Such reports have led to increased research emphasis on manual-based therapy in an effort to standardize treatment content and therapist style and reduce variability across participating therapists (Crits-Christoph et al. 1991). Manual-based therapy, which is garnering increased interest in the alcoholism treatment field, includes such interventions as behavioral marital therapy, social skills training, and cognitive-behavioral relapse prevention training. An example of rigorous research on manual-based therapy is the multisite, collaborative Project MATCH, for which three treatment manuals have been developed and disseminated to the treatment field (Project MATCH Research Group and NIAAA 1993).

The primary characteristic of counselors that influences treatment outcome appears to be interpersonal functioning, including therapists' empathy, genuineness, and respect for patients (Najavits and Weiss 1994). In a recent study of the effects of counselor style on drinking outcomes after a brief motivational interview (Miller et al. 1993), alcoholic subjects were randomly assigned to groups addressed during a single motivational feedback session in either a directive, confrontational style or an empathetic, reflective style. Confrontational behavior by the treatment counselor reliably elicited resistant patient behaviors, such as arguing, interrupting, off-task responses (e.g., inattention, silence, and sidetracking), and negative responses (e.g., blaming others, disagreeing, minimizing, and expressing unwillingness to change). The results demonstrated that confrontational counselor behavior and the associated resistant patient behaviors predicted poorer drinking outcomes 1 year after the intervention. These findings highlight the importance of the counselor's style as a main determinant of treatment outcome and demonstrate the need for further research to clarify the processes responsible for these effects.

> *The primary characteristic of counselors that influences treatment outcome appears to be interpersonal functioning, including therapists' empathy, genuineness, and respect for patients.*

Therapeutic Approaches for Comorbid Disorders

Comorbidity is the occurrence of two or more illnesses in the same person. These illnesses can be medical or psychiatric conditions, as well as drug use disorders, and can occur simultaneously or sequentially. Medical conditions that often co-occur with alcoholism are liver disease, alcoholic cardiomyopathy, and Wernicke-Korsakoff syndrome. Psychiatric disorders that are frequently associated with alcoholism are antisocial personality (ASP) disorder, depression, and schizophrenia. Because comorbid illnesses can complicate efforts to treat alcohol dependence, an understanding of these illnesses is essential to developing treatment and prevention approaches.

Psychiatric Comorbidity

Psychosocial Interventions for Comorbid Psychiatric Disorders

The rates of concurrent psychiatric disorders are high among patients in treatment for substance abuse. In a recent study of male alcoholics treated in a Veterans Administration (VA) alcoholism program (Penick et al. 1994), 36 percent had a lifetime diagnosis of depression, 17 percent of mania, and 18 percent of an anxiety disorder (obsessive-compulsive disorder, phobia, and panic attack). Among male alcoholics treated in an inpatient facility, patients with alcoholism only and those with alcoholism and depression showed comparable improvement in drinking status 1 year after treatment. However, the patients with depression showed greater overall psychiatric severity at intake and maintained that difference through posttreatment followup, regardless of their drinking reductions (Powell et al. 1992). Those results were the same as reported for an earlier study, in which the depressive symptoms of patients with alcohol dependence and either depression or depression and ASP disorder persisted in patients whose initial diagnosis was an affective disorder, despite improved drinking outcomes (Hesselbrock 1991).

An estimated one-third of schizophrenic patients have a lifetime history of alcohol abuse or dependence; almost one-half have experienced a substance use disorder (Regier et al. 1990). Patients with dual diagnoses have higher rates of relapse, poorer compliance with psychiatric medications, and increased risk for suicidal ideation and attempts (Mueser et al. 1992). A study of schizophrenic outpatients treated at a community mental health center showed that patients with a current substance use disorder used institutional services, including substance abuse and psychiatric hospitalization and incarceration, at higher rates than patients with either a past substance use disorder or no disorder (Bartels et al. 1993). These patients also used emergency services approximately twice as often as other study patients.

Research findings highlight the need for specialized, intensive services for patients with dual diagnoses, who often have cognitive and social deficits that limit their ability to participate productively in standard substance abuse treatment programs (Mueser et al. 1992). It has been suggested that long-term, flexible programs that combine elements of substance abuse (such as relapse prevention and training in social and problem-solving skills) and psychiatric treatment (such as nonconfrontational style and medication management) may optimize outcomes in patients with dual diagnoses (Mueser et al. 1992; Salloum et al. 1991).

Although the rates of personality disorders have been reported to be high among individuals with substance use disorders, these rates may partially reflect diagnostic confusion surrounding the attribution of symptomatic behavior to personality versus substance use disorders (Dinwiddie and Reich 1993). In a recent study (Penick et al. 1994), 24 percent of alcoholism treatment patients met diagnostic criteria for ASP disorder. When Nace et al. (1991) conducted a comprehensive examination for all personality disorders, 57 percent of substance abuse treatment patients met diagnostic criteria for any DSM-III-R personality disorder. The diagnoses included a high percentage of borderline, paranoid, histrionic, and passive-aggressive disorders. Patients with a personality disorder were typically younger, less educated, and more likely to be single than were patients without a personality disorder. Furthermore, personality-disordered patients were more likely to report compulsive use of alcohol, use of alcohol to manage mood and improve functioning, and greater lifetime use of illicit drugs. In general, these patients were more dissatisfied with their quality of life, including social relationships and job and school performance.

Such characteristics of personality-disordered patients have often been suggested to be predictive of poor treatment response, and it has generally been accepted that these patients show less improvement after treatment than patients with affective disorders or no psychiatric comorbidity. Longabaugh et al. (1994*b*) examined the impact of matching patients in treatment for alcoholism who had ASP disorder to cognitive behavioral or relationship enhancement interventions. Patients with ASP disorder receiving cognitive behavioral therapy reported an average of two drinks per drinking day, whereas the patients in enhanced relationship therapy reported fourfold higher drinking levels, averaging eight drinks per drinking day. Patients without ASP disorder reported approximately four drinks per drinking day regardless of treatment condition. Of particular interest (see previous discussion of patient characteristics) is that posttreatment social support for abstinence was associated with decreased alcohol use by patients without ASP disorder. For patients with ASP disorder, however, support for abstinence was associated with *increased* alcohol involvement, consistent with the tendency of patients with ASP to respond negatively to attempts at social control.

Because comorbid illnesses can complicate efforts to treat alcohol dependence, an understanding of these illnesses is essential to developing treatment and prevention approaches.

Pharmacologic Treatments of Comorbid Psychiatric Disorders

Medications that modulate brain levels of the neurotransmitter serotonin have demonstrated efficacy in decreasing depressive symptoms in patients with moderate to severe depression. These medications also may reduce drinking in depressed heavy drinkers through an improvement in mood and daily functioning. This patient-treatment matching effect is suggested by preliminary evidence of the selective effectiveness of the serotonergic medications for decreasing alcohol consumption of depressed but not nondepressed alcohol-dependent patients (Cornelius et al. 1993; Kranzler et al. 1995). Similar preliminary findings show improved drinking status for depressed alcoholics treated with tricyclic antidepressants (Mason and Kocsis 1991; Nunes et al. 1993). In light of concerns that side effects

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associated with these medications may increase treatment dropout in nondepressed patients (Kranzler et al. 1995), it is recommended that future clinical trials with these medications focus on depressed drinkers.

As described above, alcohol-dependent patients have high rates not only of depression but also of anxiety disorders. Because of the abuse liability, benzodiazepine medications generally have not been recommended for long-term treatment of anxiety disorders or alcohol consumption in persons with alcohol problems. A newer nonbenzodiazepine anxiolytic, buspirone, has received attention as a potential anticraving agent and safe treatment for anxiety in alcoholic patients. In a 12-week clinical trial of buspirone in alcoholics with high baseline levels of anxiety who were recruited through the media, the buspirone-treated subjects participated in more treatment sessions, remained in treatment longer, and were slower to relapse than placebo-treated subjects (Kranzler et al. 1995). For subjects with high baseline levels of anxiety, buspirone reduced the number of drinks per day at followup as compared with the placebo. Buspirone produced similar drinking outcomes as the placebo did in subjects with lower levels of anxiety. However, a 6-month clinical trial to determine the effects of buspirone on recently detoxified alcoholics with diagnosed anxiety disorders (Malcolm et al. 1992) showed no difference between buspirone and placebo on measures of alcohol use or anxiety. That the subjects in this study were given medication or placebo alone, without therapy, may help explain why these results differ from others. Additional research is needed to clarify potential treatment-matching effects between the effectiveness of buspirone treatment and baseline severity of anxiety and alcohol problems.

Finally, bromocriptine and nortriptyline have demonstrated efficacy in the treatment of depression and anxiety in depressed patients, and there is preliminary evidence of the effectiveness of bromocriptine for alcoholism treatment as well (Dongier et al. 1991). In a 6-month clinical trial, Powell et al. (1995) examined potential patient-treatment matching effects of bromocriptine and nortriptyline in alcohol-dependent patients as a function of baseline psychiatric status: alcohol dependence only, alcohol dependence + affective/anxiety disorder, and alcohol dependence + antisocial personality. Compared with placebo, neither bromocriptine nor nortriptyline improved drinking or mood outcomes of patients in the alcohol dependence only or alcohol dependence + affective/anxiety disorder groups. In contrast, patients in the alcohol dependence + antisocial personality disorder group taking nortriptyline showed significant improvement in several drinking measures (e.g., severity of alcohol dependence, drinking days, and abstinence at 6-month followup). Despite the study's limitations, such as small samples and many patients' meeting criteria for past drug abuse, the investigators suggested that nortriptyline reduces impulsive drinking characteristics of patients with ASP disorder through its effects on the central nervous serotonergic system, thus enabling treatment of alcoholics who have ASP disorder. (See Chapter 3, Actions of Alcohol on the Brain, for a discussion of the functions of serotonin in the central nervous system.)

Overall, these recent studies across different types of medication and comorbid psychiatric conditions highlight the importance of patient-treatment matching. They also suggest future research directions for exploring the effectiveness of other established psychiatric medications for the selective treatment of comorbid alcoholics.

Comorbid Drug Abuse and Dependence

Nicotine

The strong relationship between alcohol and tobacco use and dependence is well established. Among the general population, there is an approximately twofold likelihood of smoking cigarettes after drinking alcohol (Shiffman et al. 1994). Estimates of smoking prevalence among alcoholics generally range from 75 to 90 percent (Burling and Ziff 1988; Istvan and Matarazzo 1984; Toneatto et al. 1995), a rate approximately threefold higher than among the general population. Whereas the rates of smoking have declined in the general population, rates among heavy drinkers have not. Indeed, some investigators have suggested that smoking can now be considered a marker for risk of heavy alcohol use. Finally, in addition to higher prevalence rates, heavy drinkers also smoke more cigarettes per day and have higher levels of nicotine dependence, as evidenced by higher scores on standardized measures of nicotine

... some investigators have suggested that smoking can now be considered a marker for risk of heavy alcohol use.

dependence and shorter latency to first cigarette smoked on waking (Abrams et al. 1992; DiFranza and Guerrera 1990; Joseph et al. 1990; Kozlowski et al. 1989; Orleans and Hutchinson 1993).

Although the negative health consequences of tobacco use for smokers are well documented (Centers for Disease Control 1990), increased attention has been given to the need for tobacco interventions among alcohol-dependent persons as the result of two findings. First, there is strong evidence of a synergistic interaction between alcohol and tobacco that increases the risk for hypertension and certain types of cancers (e.g., oral cavity, esophagus, and larynx) above the risks of either alcohol or tobacco alone (Groppelli et al. 1992; Wynder et al. 1977). Second, establishment of the health hazards of second-hand smoke (Glantz and Parmley 1991) has led to increased restriction of smoking in public facilities, a trend particularly apparent in health care facilities. In 1992, the Joint Commission on Health Care Organizations moved to ban smoking in hospital settings.

The alcoholism treatment field has been slow to respond to the exceptionally high rates of tobacco use and the escalating public health concerns for the alcoholic smoker. Most often, alcoholism treatment facilities have continued to accept, and have even promoted, smoking as a means to help to reduce stress during recovery. Several explanations have been offered for this position (Goldsmith et al. 1991). First, a widespread concern is that concurrent efforts to establish abstinence from tobacco and alcohol or other drug use would be too difficult and would accelerate relapse for both dependencies. Because nicotine dependence is perceived as the less serious addiction, initial efforts have focused on cessation of alcohol or other drug use. Second, a more pragmatic concern is that alcohol-dependent patients would not accept substance abuse treatment in smoke-free facilities, thus undermining admission rates and the financial stability of the programs. Third, smoking is prevalent among the staff of many addiction treatment facilities. There often has been little impetus to initiate smoking bans for patients when the bans would clearly have an impact on staff members' opportunity to smoke.

Two recent laboratory studies have demonstrated that people have an increased urge to smoke in simulations of high-risk alcohol use situations and found a positive association between the urge to drink and smoke, particularly during exposure to alcohol. These studies also found that more severely nicotine-dependent patients have increased responsiveness to alcohol-related cues. Collectively, these studies indicate that cigarette use may act as a trigger or cue for alcohol relapse in recently treated alcoholics (Abrams et al. 1992; Gulliver et al. 1995).

A series of ground-breaking surveys and smoking cessation trials with substance-dependent patients have addressed such concerns. Joseph et al. (1990) found that even when smoking was still allowed on a residential alcoholism treatment unit, approximately one-third of new admissions expressed interest in receiving smoking treatment during their stay for alcoholism treatment. After the unit became smoke-free, the number of patients expressing interest in participating in a smoking cessation program nearly doubled. Orleans and Hutchinson (1993) reported that among patients surveyed during residential treatment, 83 percent indicated a desire to stop smoking, with 63 percent expressing moderate interest and 42 percent expressing strong interest in antismoking treatment during their hospital stay. Approximately two-thirds reported one or more serious attempts to quit smoking in the past; almost one-half reported attempting to quit in the last year. When asked to rate the possible barriers to successfully stopping smoking, fewer than 10 percent of the patients identified maintaining sobriety or increased alcohol or other drug use as a significant barrier.

A survey of 19 facilities (Goldsmith et al. 1991) identified as having implemented smoking restrictions during the mid-to-late 1980s showed that in contrast to the staff beliefs about implementing a smoking ban, facility directors reported from none to few complaints regarding the restrictive smoking policy. They reported only minor impact of the policy on patient admissions and retention; furthermore, they reported success in decreasing or eliminating smoking among patients during their residential treatment. Smoking cessation interventions implemented by these facilities included educational lectures on nicotine dependence, reading materials and handouts, diet and exercise advice, and group therapy. In addition, some units provided pharmacologic support with nicotine gum or patches for nicotine withdrawal.

A recent study examined the effects of both pretreatment and posttreatment smoking status on abstinence from alcohol and other drugs after outpatient substance abuse treatment (Toneatto et al. 1995). The results showed that when subjects had higher levels of nicotine dependence (as indicated by smoking the first

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cigarette of the day within 5 minutes of waking) before treatment for alcoholism, they had significantly more heavy-drinking days posttreatment than either ex-smokers or subjects with lower levels of nicotine dependence. Moreover, subjects who decreased their cigarette use during the posttreatment period reported more and longer periods of alcohol abstinence than subjects who increased their smoking levels.

In a quasi-experimental study, researchers at the Minneapolis VA hospital (Joseph et al. 1990) examined the effects of an indoor smoking ban and a mandatory smoking treatment program on treatment retention and smoking cessation for patients in residential alcoholism treatment. Rates of early discharge after implementation of the smoking ban were unchanged. More than 40 percent of the patients treated after the ban reported abstaining from cigarette use for more than 1 week compared with only 9 percent before the ban. In followup interviews conducted 8 to 21 months after treatment, patients treated after the ban reported slightly higher rates of smoking abstinence than patients treated before implementation of the smoking interventions as well as comparable rates of abstinence from alcohol and other drugs (Joseph et al. 1993).

Subjects who decreased their cigarette use during the posttreatment period reported more and longer periods of alcohol abstinence than subjects who increased their smoking levels.

Finally, in a prospective controlled trial, Hurt et al. (1994) examined the effects of a standardized nicotine-dependence intervention conducted with alcoholic patients in a residential treatment facility that included an individualized nicotine treatment consultation, 10 group education and therapy sessions, and a relapse-prevention protocol, with telephone calls and letters after the patients were discharged. Only one-quarter of the patients who met study criteria agreed to participate in the smoking intervention, indicating limited acceptance of voluntary cessation interventions by alcoholic patients. One year after discharge from residential treatment, 12 percent of the intervention patients and none of the control patients were confirmed to have stopped smoking. Nicotine dependence intervention did not seem to interfere with abstinence from other drugs: At 1-year followup, 69 percent of the intervention patients and 66 percent of the control patients reported abstinence from alcohol and other drugs.

Other Drugs

Among people seeking treatment for alcoholism, the rates of other drug misuse is estimated at 40 percent (Rush and Ekdahl 1990). Besides alcohol, the most frequently misused substances are marijuana, cocaine and other stimulants, opiates, sedatives, phencyclidine (PCP), and hallucinogens (Miller and Giannini 1991). In a recent survey of alcohol and other drug treatment agencies in California, more than 80 percent of patients in alcoholism treatment reported the use of at least one additional drug; almost 30 percent reported using four or more drugs (Weisner 1992). Most of the drug misuse reported by these patients occurred in combination with alcohol ingestion. The patients were at least as likely to attribute problem indicators (e.g., used more than intended, could not cut down or stop, interfered with life roles, but no withdrawal symptoms) to drug use or combined alcohol and other drug use as to alcohol use alone (Weisner 1992).

The increased prevalence of and problems associated with other drug use by alcoholism treatment patients have stimulated the research community's interest. As a result, increased research efforts are aimed at characterizing the polysubstance-abusing treatment-seeking population and examining the effects of multiple substance abuse on treatment outcomes.

In a study of admissions to a 28-day traditional rehabilitation program (Brown et al. 1993), patients who abused only alcohol were significantly older and more likely to be married or living in a common-law relationship than patients who abused both alcohol and cocaine. These alcohol-only patients reported significantly longer periods of alcohol use and more severe alcohol-related problems at the time of admission to treatment. In addition, Brower et al. (1994) found that alcohol-only rehabilitation patients had an increased severity of psychiatric disorders and were more likely to have had prior treatment for their substance use disorders than either patients who used cocaine only or patients who used alcohol and cocaine.

Several studies have suggested diminished treatment efficacy for polysubstance-abusing patients enrolled in alcoholism treatment facilities (Mammo and Weinbaum 1993; Wickizer et al. 1994). For example, patients abusing both alcohol and cocaine were more likely to report alcohol or drug relapse and fewer abstinent days than alcohol-only patients during the 6 months after discharge from treatment (Brown et al. 1993). Urinalysis at followup corroborated the patients' self-reports; specifically, 30 percent of the specimens from patients who had used alcohol and cocaine were positive at followup compared with 6 percent of the specimens from patients who had used alcohol only. Similar findings of decreased treatment efficacy for patients with multiple substance use disorders by other investigators (Brower et al. 1994; Carroll et al. 1993) generally suggest the need for more tailored and intensive treatment interventions to address the unique relapse risks associated with different drugs.

Patient-Treatment Matching

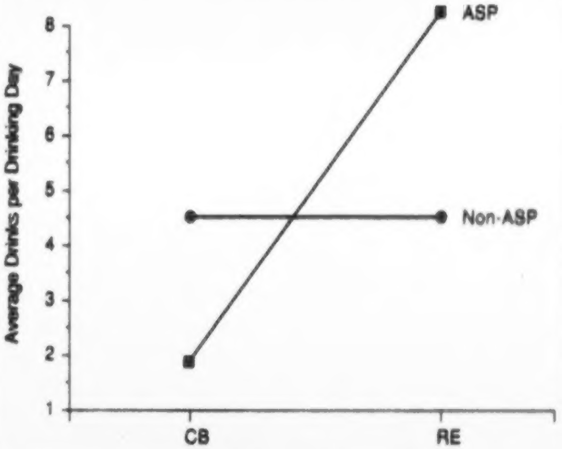
As highlighted earlier, no single alcoholism treatment has emerged as clearly superior to all other types of treatment for heterogeneous groups of alcohol-dependent patients. Thus, there continues to be considerable interest and progress in the use of patient-treatment matching research designs to explore the differential effectiveness of specific treatment interventions in targeted subpopulations of alcoholic patients. Several patient characteristics have been explored as possible bases for treatment matching: demographic characteristics, such as gender and age; alcohol-related characteristics, such as drinking severity and family history of alcoholism; psychological status, such as psychiatric diagnoses, personality traits, and overall level of psychological functioning; and social functioning (Mattson et al. 1994).

Recently, increased emphasis has been placed on the type and specificity of treatment interventions studied with regard to matching. Candidate treatment interventions have been selected for study on the basis of differing intensity (e.g., inpatient, outpatient, and brief intervention), format (e.g., group, individual, and family therapy), philosophical model (e.g., medical, psychosocial, and AA), and specific therapeutic content (e.g., cognitive/behavioral, interactional, and motivational enhancement) (Donovan et al. 1994). The diversity in the patient characteristics and treatment interventions that have been examined by using a matching paradigm has had the benefit of generating a wide range of initial findings for followup in future investigations. To date, however, only a few matching relationships have been demonstrated consistently across studies as a sound basis for clinical decisions. In Project MATCH, NIAAA is supporting a large-scale, randomized clinical trial to assess the overall value of matching as a treatment strategy. The multisite trial is examining the relative effectiveness of several widely implemented clinical interventions with different types of alcohol-abusing clients (Project MATCH Research Group and NIAAA 1993).

The most robust patient-treatment matching relationship to emerge from recent research is the differential effectiveness of skills-oriented therapy, compared with interpersonally oriented therapy for the treatment of patients who have sociopathic tendencies (Cooney et al. 1991; Kadden et al. 1989; Litt et al. 1992; Longabaugh et al. 1994*b*). In the most recent of these studies, outpatient alcoholic patients were characterized by the presence or absence of a DSM-III-R diagnosis of ASP disorder (Longabaugh et al. 1994*b*). Patients were randomized into a 20-session program of either individually focused cognitive behavioral therapy, designed to identify the high-risk cues to drinking and to restructure cognitions and consequences of drinking, or an interpersonally focused therapy known as relationship enhancement therapy, designed to teach techniques to help the relationship reinforce abstinence and deal with relapses. Treatment retention and participation were similar for patients with and without ASP disorder in both treatment programs. As shown in figure 2, the results demonstrated a positive treatment matching effect: ASP patients treated with individually focused cognitive behavioral therapy reported having fewer drinks per drinking day than did ASP patients treated with relationship enhancement therapy or non-ASP patients in both treatment conditions. In light of the generally poor prognostic status associated with the diagnosis of ASP disorder (Rounsaville et al. 1987; Schuckit 1985), these findings are particularly exciting. Generally, across studies, it appears that alcohol abusers with sociopathic tendencies achieve better outcomes when therapies teach individually implemented alcohol-specific skills rather than when they stress social support for abstinence.

Another strong predictor of treatment response appears to be the overall severity of psychiatric symptomatology (McLellan et al. 1983). Pettinati et al. (1993) have reported that patients with an increased severity of psychiatric disorders were retained in treatment longer in the inpatient setting than in the outpatient setting.

Figure 2. Average number of drinks per drinking day among alcohol abusers with and without antisocial personality (ASP) disorder as a function of the interaction of ASP diagnosis and treatment focus, either cognitive behavioral (CB) therapy or relationship enhancement (RE) therapy, at 7–12 months (untransformed scores).



Source: Longabaugh et al. 1994*b*. Reprinted by permission. Drinking outcomes of alcohol abusers diagnosed as antisocial personality disorder. *Alcoholism: Clinical and Experimental Research* 18(4): 778–785, 1994.

It is also interesting that, as described earlier (see the section on pharmacologic treatments of comorbid psychiatric disorders), several investigators have now suggested that selective effectiveness of pharmacologic agents is a function of the baseline psychiatric symptoms of study participants. For example, serotonergic medications have been found to decrease alcohol consumption of depressed but not nondepressed alcohol-dependent patients (Cornelius et al. 1993; Kranzler et al. 1995). Patients with major depression secondary to alcoholism responded well to treatment with the antidepressant drug desipramine and maintained abstinence significantly longer than depressed patients receiving placebo (Mason et al. 1996). Treating depression secondary to alcoholism may be important in reducing risk of drinking relapse. Similarly, the antianxiety agent buspirone has been shown to improve drinking status at followup only in those subjects with high baseline levels of anxiety, not in nonanxious subjects (Kranzler et al. 1995). These findings suggest that psychiatric symptomatology and severity can exert an important influence on treatment outcomes of alcoholic patients and should be considered in patient-treatment matching efforts.

In current clinical practice, several newer strategies represent an effort to guide admission decisions for existing treatment modalities. For example, the patient placement criteria disseminated by the American Society of Addiction Medicine (ASAM) (Hoffman et al. 1991) represent a comprehensive set of guidelines to direct decisions concerning patient admissions to available treatment using standardized, objective specifications. Patient-matching variables include acute intoxication and withdrawal symptoms, medical and psychiatric status, alcohol dependence severity, prior treatment and relapse history, and psychosocial functioning. Treatment-matching variables include setting, staffing patterns, types of therapies, and ancillary support systems.

A recent evaluation of these criteria with male alcohol- and cocaine-dependent veterans (McKay et al. 1992) involved sorting patients into the categories recommended for inpatient versus intensive outpatient placement by using ASAM criteria. However, all patients received treatment in an intensive outpatient program. Those who would have been assigned to inpatient treatment according to ASAM criteria, but were actually mismatched to intensive outpatient treatment, demonstrated treatment retention and outcomes comparable with those of patients assigned to and treated in intensive outpatient services. Once guidelines are successfully developed and empirically validated, they may be of substantial benefit to treatment providers making placement decisions, to insurance companies monitoring patient placement, and to researchers interested in treatment evaluation (Institute of Medicine 1990).

Summary

In the 3 years since publication of the *Eighth Special Report to the U.S. Congress on Alcohol and Health*, considerable progress has been made in several areas of alcoholism treatment. The approval of naltrexone for the treatment of alcoholism represents a breakthrough in pharmacotherapy for alcoholism by directly addressing one of the potential biological bases of the addiction; that is, the interaction of alcohol and endogenous opioid receptor activity. This ushers in a new era of pharmacologic interventions for the alcoholism treatment field—one based on a growing understanding of the scientific bases for drug reinforcement and craving.

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Considerable progress is still being made in understanding the important role of social support in the alcohol recovery process and in designing assessment instruments and specialized treatment interventions to measure and mobilize this support. A notable finding is that socially based therapies are not universally effective and should be carefully targeted to persons with high social investment and supportive social networks.

More generally, patient-treatment matching continues to emerge as the cornerstone of treatment selection decisions. Recent studies have demonstrated the importance of specific psychiatric diagnoses, such as depression and ASP disorder, as well as global psychiatric severity ratings as key matching characteristics to maximize psychosocial and pharmacologic treatment effectiveness. Research also has identified patients' readiness for change as a strong predictor of treatment response and an important basis for intervention selection.

In other areas of research, the groundwork has been laid for scientific advancements over the next several years. The APA has published its revised diagnostic manual, DSM-IV, which includes substantive changes in the diagnostic criteria for alcohol dependence and abuse. Emerging research on the impact of these changes and comparisons with other widely used diagnostic systems will help to illuminate the theoretical underpinnings of the diagnostic system as well as provide practical information to guide clinical and reimbursement decisions.

In related developments, biomedical research has added a focus on the patient's quality of life as central to the determination of overall treatment effectiveness. In the alcoholism treatment field, specialized assessment instruments have been developed to measure intrapersonal and interpersonal functioning and other person-environment areas relevant to alcoholism recovery. These tools promise to enrich research findings for years to come.

Finally, clinical and research attention has turned to issues of comorbidity of alcoholism and other psychoactive substance abuse and the impact of comorbidity on treatment effectiveness. Of particular interest is the growing body of evidence that cigarette smoking can and should be addressed in the context of alcoholism treatment programs. Recent findings suggest that alcohol abstinence may be facilitated rather than undermined by simultaneous smoking cessation, as popular beliefs have suggested. This area will be critical for research as treatment programs and staff struggle with implementation of no-smoking policies in the upcoming years.

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Chapter 11

Alcohol Health Services Research

Introduction

Alcohol health services research is an emerging field of alcohol research with the ultimate aim of improving *accessibility*,[1] quality, effectiveness, and cost-effectiveness of alcohol prevention and treatment services through the systematic study of how they are organized, managed, and financed. Alcohol research has made considerable strides in identifying efficacious approaches to the prevention and treatment of alcohol abuse and dependence (see Chapter 9, Prevention of Alcohol Problems, and Chapter 10, Treatment of Alcoholism and Related Problems) through studies primarily conducted in controlled experimental settings. The focus of alcohol health services research is to explore the effectiveness of these interventions in real-world settings and identify the organizational, managerial, and financial factors that facilitate or hinder their access or implementation. Research on these factors takes on increased importance in light of the current concern about controlling the rise in health care expenditures. Thus, it is now both timely and important to develop new knowledge of the factors that facilitate or hinder alcohol services delivery in actual practice settings.

Alcohol health services research is a multifaceted field of inquiry that encompasses a variety of disciplines and includes descriptive studies of the organization and financing of the Nation's alcohol treatment system as well as field experiments that test different organizational, financial, and therapeutic approaches to the treatment of alcohol dependence. This chapter summarizes the findings of published alcohol health services research. Beginning with a discussion of features that distinguish this field from other areas of alcohol research and a brief description of its legislative and substantive origins, the chapter presents major findings in light of four key questions of particular interest to health services researchers and policymakers. The chapter concludes by offering recommendations for future research on alcohol treatment and prevention services.

Distinctive Features

Alcohol health services research can be distinguished from other areas of alcohol-related research by several characteristics. First, alcohol health services research emphasizes the study of alcohol treatment and prevention services as they are delivered in real-world settings as opposed to specialized experimental settings, such as controlled clinical trials.[2] Health services researchers are concerned with how well interventions shown to be efficacious in specialized experimental settings work when carried out in everyday practice settings, where there is considerably less control over who delivers the treatment, who receives the treatment, and the treatment setting. Accordingly, questions about the effectiveness of alcohol-related interventions include a broader range of variables than are typically investigated in controlled clinical trials. These variables include financing, organizational structure, treatment process, management strategies, and the wider environment of the community and its institutions. Among the key issues for researchers are access to, *availability* of, and costs of services; long-term clinical outcomes; and patient satisfaction.

Conducting research in real-world settings means including the various stakeholders in the treatment process, such as practitioners, administrators, and policymakers, in the development of research questions and the implementation of research protocols. A research design that will provide information generalizable to the practice of treatment is of utmost importance. The development of rigorous research designs and measurement systems in less-than-ideal research settings is both the hallmark of alcohol health services research and its major challenge.

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[1] For a definition of *accessibility* and other terms in this chapter, see the glossary.

[2] During the 1990s, treatment for alcohol and drug dependence has been almost totally combined. Research discussed in this chapter refers to those combined programs unless designated otherwise.

A second distinctive feature of alcohol health services research is its focus on factors both proximal to and farther removed from the recipient of care. At the clinical level, researchers assess the nonmedical factors that influence client outcomes, such as access to care, length of stay, and type of treatment setting. At the institutional level, the focus is on the organizational and administrative structures of treatment and how these factors influence patient access and treatment outcome. For example, alcohol health services researchers would examine the impact of utilization review mechanisms or alternative approaches to financing services on the costs and utilization of services. At the systems level, investigators concentrate on the interrelationships between different facets of the health care system and other health and social service institutions examining, for example, *cost shifting* from the health care system to criminal justice when services are limited. An important research question might be: Are treatment outcomes better when clients of the criminal justice system are referred to a specialized alcoholism treatment setting than when they are treated within the jail setting? Finally, at the environmental level, health services research addresses the larger social, political, and economic contexts that affect alcohol health services. A key research question at this level might be: Do legislative mandates for insurance coverage of alcohol treatment result in increased use of services by those who need them?

Health services research addresses the larger social, political, and economic contexts that affect alcohol health services.

A third distinctive feature of alcohol health services research is its multidisciplinary nature. Examination of a broad set of variables and multiple analyses requires that the research draw on such disciplines as medicine, psychology, economics, sociology, epidemiology, and management science.

Origins

Alcohol health services research is rooted in different legislative and advisory group initiatives. First, an amendment to the 1974 Public Health Service Act amendment created the National Center for Health Services Research (now known as the Agency for Health Care Policy and Research) to collect data and develop methods to monitor national health care use and costs. Subsequently, a congressional advisory panel recommended assessment of national needs for services to address abuse of alcohol and other drugs and for mental health services. At the same time, a National Academy of Sciences report (Institute of Medicine [IOM] 1979) defined the significant parameters of alcohol health services research. Finally, Section 409 of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) Reorganization Act of 1992 requires that the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and other ADAMHA (now the Substance Abuse and Mental Health Services Administration [SAMHSA]) Institutes devote 15 percent of their research portfolios to health services research.

Epidemiologic and clinical studies cosponsored by NIAAA have contributed to the development of the alcohol health services research field. For example, the National Drug and Alcoholism Treatment Utilization Survey (NDATUS) (Reed and Sanchez 1986) has provided data on treatment capacity, utilization rates, and staffing patterns of facilities that provide alcohol and other drug services. These data provided the framework for development of appropriate types of services and approaches to measuring service costs. An extensive program of research on the epidemiology of alcohol, other drug, and mental health problems has added valuable data on the use of services in a variety of treatment settings (e.g., the National Longitudinal Alcohol Epidemiologic Survey [NLAES], National Alcohol Survey, and National Hospital Discharge Survey).

Finally, results from the general health services research field have identified issues important to the alcohol field, including the effects of different types of health insurance, deductibles, and coinsurance on use of health care services; the implementation of diagnosis-related groups (*DRGs*) in Medicare reimbursement; risk adjustment; and patient satisfaction. In addition, major studies conducted in the health services research field, such as the RAND Corporation's Health Insurance Experiment (Wells et al. 1991) and the Medical

Glossary

Accessibility—Refers to the extent to which individuals can obtain available alcohol services. There are many types of accessibility, including geographic accessibility (are services located within a reasonable distance from clients' homes?), financial accessibility (can clients afford services?), and psychological/cultural accessibility (are services organized and presented in a manner that is consistent with a client's cultural background?).

Appropriateness—The degree to which the services provided are relevant to a client's needs, given the current state of knowledge.

Availability—Usually refers to the supply of services for a given disorder (e.g., number of treatment beds, hours of operation, or number of treatment providers). It is important to distinguish availability from *accessibility*. A service may be available but not accessible.

Capitation—A fixed rate of payment to cover a specified set of health services for an enrolled population usually provided on a per member per month (PM/PM) basis. Thus, capitation refers to the form of payment to a health provider for services rendered, regardless of the level of utilization of services.

Carve out—A program separate from the primary group health plan designed to provide a specialized type of care, such as treatment for alcoholism. In the alcohol and other drug field, carve outs are usually referred to as "behavioral health carve outs." Carved-out plans are usually administered by a specialty vendor.

Copayment—A fee charged to consumers at the point of service to cover the administrative costs associated with office or pharmacy visits.

Cost shifting*—Refers to the redistribution of payment sources. For example, cost shifting occurs when a provider makes up for a lower rate of reimbursement from one payer by increasing the rate of reimbursement from another payer.

DRGs—Diagnostic-related groups. Any system of classifying patients according to categories of diagnosis that should require similar treatment interventions. DRGs are currently used to determine the amount Medicare reimburses for hospital stays. Medicare's DRGs were developed at Yale University in 1975 and have been adopted by most States in their hospital reimbursement rate-setting programs.

Employee assistance program (EAP)—A program of counseling and other forms of assistance to employees suffering from alcoholism, substance abuse, or emotional or family problems.

Fee for service—Fee-for-service reimbursement is the traditional provider reimbursement method under which the provider receives a payment calculated on the basis of the provider's billed charge.

HMO—A health maintenance organization, which, for a prepaid fee, provides comprehensive health care to a voluntarily enrolled membership. The following are four of the many varieties of HMOs:

Staff Model HMO—Employs its own physicians to provide health care to enrollees. Generally, all ambulatory health services are provided under the one roof, and all premiums and other revenues assure that the HMO physician employees are compensated by salary and incentive programs.

Group Model HMO—Involves a contract between large multispecialty group practices and an HMO. Reimbursement is made on a capitated basis.

Network Model HMO—Consists of a network of group practices.

Independent Practice Association Model—Comprises individual providers or small groups that provide care through capitated contracts or discounted fee-for-service arrangements. Physicians maintain their own private practice and contract with multiple types of managed care organizations.

Independent practice association (IPA)—A group of physicians who have formed an association as a separate legal entity for the purpose of managed care contracting to provide services in their own offices. IPA members are compensated on a *capitation* basis for contracts with IPA model *HMOs* or a *fee-for-service* basis for medical services provided to members of other types of managed care plans.

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*In this chapter, cost shifting also means the shifting of costs to other medical services, such as emergency room or general medical, or even to other systems, such as welfare or criminal justice, when adequate alcoholism treatment is not available.

Outcomes Study (Tarlov et al. 1989), have provided preliminary data on the effects of some alternative financing approaches on costs and utilization of health services.

This chapter presents research findings that address four questions central to the delivery of alcohol treatment services:

1. What is the availability of alcohol treatment services?
2. What factors influence access to and use of alcohol health services?
3. What are the costs of alcohol-related problems and alcohol health services?
4. What is the cost-effectiveness of alcohol health services?

Although alcohol health services research is actively investigating these important issues, it does not have the same longstanding history of research in the alcohol field as do such other areas as biomedical, epidemiologic, and clinical research. Thus, much of its important work to date has involved descriptive studies that have set the stage for the explanatory studies that are now underway. The following sections describe the four central issues in alcohol services research, their implications for policy and clinical decisionmaking, and research findings to date. Chapter 9 presents findings concerning a fifth, and very important, alcohol health services research question—the effectiveness of ***prevention*** services.

Availability of Alcohol Treatment Services

Alcohol health services research addresses the availability of treatment services for different population groups and for persons living in different geographic areas. Among other issues, important concerns include whether treatment is available (1) for individuals living in both rural and urban areas, (2) for individuals with and without health insurance coverage for alcohol health services, and (3) for population groups who may have special treatment needs (e.g., pregnant women or adolescents). Questions of treatment availability become more complex when the focus is on particular types or settings of treatment; for example, whether inpatient treatment is available for clients in both the public and the private sector.

Many crucial policy decisions require answers to these questions. The assessment of available services prior to dramatic shifts in health care policy is important to the evaluation of new service organizations. The availability of services is fundamentally related to understanding barriers and incentives to access. For example, how is availability of services affected by the transition of services from the public sector to private contracting? More specifically, do various types of managed care organizations (MCOs) have different effects on the availability of services in the private and public sectors? Answers to these questions will form the basis of State, employer, and insurer arrangements with MCOs. With the gradual consolidation of MCOs within geographic areas come expectations that these organizations will assume responsibility for the overall health status of groups of individuals. Thus, the availability of services becomes important to MCOs as well as to State and Federal government alcohol and drug abuse agencies.

The following factors are key to understanding the availability of alcohol treatment services:

- Federal and State policy (e.g., the merging of alcohol and other drug treatment, mandated insurance coverage, and set-asides for services for pregnant substance abusers)
- Organization and financing of treatment services in the public and private sectors, especially within MCOs
- Provision of alcohol-related health and social services not related to specialty treatment

Data Sources

Much of what is known about the national alcohol treatment system and its population over time comes from NDATUS—a census of public and private programs (NIDA 1993) conducted intermittently since 1979 and annually beginning in 1990. Although it has limitations (Schmidt and Weisner 1993), the survey remains extremely valuable for assessing treatment availability across the country.

The most current NDATUS available (1993)[3] reported 1,087 units (9.5 percent of total units) as alcohol-only treatment facilities, 9,379 (81.6 percent) units as combined alcohol and other drug treatment facilities, and 1,030 (9 percent) units as drug-only treatment facilities.

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[3] The data are from a special analysis of the 1993 NDATUS performed by the Substance Abuse and Mental Health Services Administration (SAMHSA) for this report. NDATUS is now known as UFDS (Uniform Facililty Data Set).

Table 1. Units and clients[*] in programs for treatment of abuse of alcohol, of other drugs, or of alcohol and other drugs in 1982, 1987, 1990, and 1993, National Drug and Alcoholism Treatment Utilization Surveys (NDATUS).

	1982		1987		1990		1993	
Type of Unit	**Units % (N)**	**Clients % (N)**	**Units % (N)**	**Clients % (N)**	**Units % (N)**	**Clients % (N)**	**Units % (N)**	**Clients % (N)**
Alcohol only	51 (2,729)	(199,492)	25 (1,708)	22 (136,917)	13 (1,104)	17 (132,093)	10 (1,087)	11 (102,386)
Drug only	26 (1,514)	NA[†]	16 (1,075)	24 (144,446)	11 (976)	17 (126,947)	9 (1, 030)	13 (121,920)
Alcohol and drug combined	26 (1,504)	(83,677)	59 (4,083)	54 (332,760)	76 (6,662)	66 (508,789)	82 (9,379)	76 (719, 902)
Total	(5,747)	NA	(6,866)	(614,123)	(8,742)	(767,829)	(11,496)	(944,208)

[*] Sample sizes are in parentheses. Combined percentages may not sum to 100% due to rounding error.

[†] Data on client utilization for drug-only units were not available in 1982 reports of the NDATUS.

Sources: Schmidt and Weisner 1993 (p. 351) for 1982, 1987, and 1990; a special analysis of the 1993 NDATUS by the Substance Abuse and Mental Health Services Administration for this report for 1993. Schmidt and Weisner 1993 is reprinted by permission.

The treatment capacity for each type of facility was 136,957, 984,861, and 150,149 clients, respectively. The data showed that *on a given day*, 102,386 clients used alcohol-only treatment facilities (10.8 percent of total clients), 719,902 clients used combined alcohol and other drug treatment facilities (76.2 percent), and 121,920 clients used drug-only treatment facilities (12.9 percent). Of the alcohol only and combined alcohol and drug treatment facilities, 17.8 percent had public ownership, 61.2 percent had private-nonprofit ownership, and 21 percent had private-for-profit ownership in 1993.

Examining changes in treatment units over time provides an opportunity to document changes in the availability of treatment. For example, NDATUS data used to examine trends in availability between 1982 and 1993[4] show a 147-percent increase (from 4,233 to 10,466) in the number of alcohol only and combined alcohol and drug treatment units and a 190-percent increase (from 283,169 to 822,298) in the number of clients served on a given day (table 1). Examining changes between 1982 and 1990, Schmidt and Weisner (1993) found increases of 68 percent in treatment units providing early intervention services, 82 percent in programs that included self-help groups, 57 percent in programs to discourage drinking and driving, and 77 percent in *employee assistance programs*. Analysis of 1982–1992 NDATUS data showed an increase in the percentage of programs offering specialized services for women, from 23 percent in 1982 to 53 percent in 1992 (Schmidt and Weisner 1995).

Service Availability Across States

Several studies have shown variation in availability of treatment for alcohol and other drug problems from State to State. An analysis by the IOM (1990) of funding levels, overall treatment capacity, and capacity by public versus private sectors showed substantial variation by State but gave no indication that higher private capacity was related to lower public capacity. Huber et al. (1994) also found large differences among States in both the proportion of the population in treatment and the proportion of funding per client. Treatment capacity was very uneven across States, especially for clients in the public sector. Moreover, availability across States fluctuated over time, predominately in relation to larger economic factors. The IOM analysis found little relationship between allocated capacity for alcohol treatment by State and need-based social indicators, such as age-adjusted mortality from cirrhosis and per capita consumption of alcohol. The study attributed this disparity between need and capacity partly to the lack of a needs-based approach for resource allocation across funding sectors.

The availability of certain types of services also varies greatly depending on whether the program is public or private. Researchers have documented the development of a "two-tiered" system of care consisting of public and private programs with different amounts of funding and types of services (Wheeler et al. 1992; Yahr 1988). Alcoholism treatment programs with public ownership had fewer medical and inpatient services than those with private ownership. Of the total program units, the proportion of publicly owned programs available decreased from 28 to 18 percent between 1982 and

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[4] It is important to note that in 1993, all nonrespondents to the survey were contacted, and at the least, minimum data were obtained.

1990, while the proportion of for-profit programs increased from 7 to 18 percent (Schmidt and Weisner 1993). Private not-for-profit agencies maintained a consistently strong presence, representing about two-thirds of the system, but their funds from the private sector and private clients increased proportionately during that time. The availability of different types of services and settings (e.g., prevention, inpatient, outpatient, and detoxification) and the variety of ancillary services available to support treatment (e.g., child care) differed also.

Because public dollars allocated for alcohol and other drug abuse treatment are fixed and public-sector services are limited, clients are often assigned to waiting lists when treatment programs are unavailable (Rogowski 1992). A national survey of agencies providing outpatient drug treatment and combined alcohol and drug treatment showed that ownership status is related to the availability and number of services offered (Wheeler et al. 1992). In the overall distribution of services, public, private nonprofit, and private for-profit programs, in that order, provided the largest proportion of individual sessions and the most hours of service, as well as the most time per individual session. This pattern, however, was reversed for group therapy. Both the time spent in group therapy sessions and the number of sessions provided per week by private for-profit programs exceeded those for nonprofit and public programs (Wheeler et al. 1992).

Mandated set-asides have greatly affected the availability of alcohol treatment services in the public sector.

Factors Affecting Availability of Services

Alcohol health services researchers have examined several factors that affect the availability of alcohol services. These factors include social policy, the organization and financing of treatment, and the use of services outside the alcohol treatment system.

Social Policy

Factors relating to social policy include legislative mandates for insurance coverage and for funding set-asides for specialized services, such as those for pregnant alcohol and other drug abusers. Much of the growth in services in the private sector has been attributed to State legislation regarding insurance coverage of alcohol treatment (IOM 1990; Schmidt and Weisner 1993). By 1991, 41 States had addressed the availability of insurance coverage for alcohol treatment, legislating mandates for coverage by private insurers. Twenty-three States required the insurer to provide coverage in each of the plans, and 18 States required the insurer to offer coverage to purchasers. This differed from earlier times when many plans did not offer alcohol treatment as a part of the benefit. The mandates did not legislate requirements for providing treatment to the uninsured. Furthermore, the Health Maintenance Organization Act of 1973 required all health maintenance organizations (*HMOs*) receiving Federal assistance to provide alcoholism treatment services. A 1982 study of all HMOs showed that more than one-half provided alcohol and other drug treatment services (Levin et al. 1984). The 1988 Employee Benefits Survey of medium- and large-size firms demonstrated that all HMO insurance plans provided coverage for some form of treatment for alcohol abuse (Jensen and Morrisey 1991). In 99 percent of plans, alcohol treatment, in some form, was explicitly covered. Forty-eight percent of the plans covered inpatient rehabilitation, whereas all plans covered outpatient services.

Policy decisions in the private sector also influence the health care marketplace and indirectly affect treatment capacity. For example, in 1981, the National Association of Insurance Commissioners adopted a model benefit; that is, a recommended set of benefits for alcohol treatment. It included 30 days of inpatient care and 30 outpatient visits per year. This model influenced the increase of treatment programs as well as the availability of inpatient programs (Scott et al. 1992).

Mandated set-asides have greatly affected the availability of alcohol treatment services in the public sector. Block grant legislation was enacted in 1981, bringing with it set-asides for special populations and services, but this also reduced the flexibility of States to provide services (Schmidt and Weisner 1993). This legislation has been amended more than 15 times with new or adjusted set-asides (U.S. General Accounting Office 1995). The initial set-asides were 35 percent each for alcohol treatment and drug treatment and 20 percent for prevention. A 5-percent set-aside mandated in 1984 for women's services was increased to 10 percent in 1988. The 1992 revisions emphasized programs for pregnant women, individuals who inject drugs, and individuals with human immunodeficiency virus or tuberculosis, as well as prenatal and child care and outreach programs. Thus, the publicly funded alcoholism treatment system now serves women, adolescents, injection drug users, and individuals referred from the courts for alcohol-related offenses, such as drinking and driving or domestic violence (IOM 1990).

Organizational Factors

The availability of alcohol treatment services is affected by the way services are organized (e.g., MCOs versus private *fee-for-service* organizations) and interorganizational factors (e.g., the merging of alcohol and drug treatment systems). The predominant organizational factor currently affecting overall availability of services and the types of services available is the dramatic growth and diversification of MCOs. One study showed that MCOs covered 51 percent of privately insured individuals in 1993, and enrollment was increasing (Gabel et al. 1994). At the same time, the managed care industry is undergoing a period of consolidation. According to industry reports, in 1993, the 17 largest managed behavioral health companies together covered about 80 million people (Freeman and Trabin 1995). Although the main organizational models of coverage are in a period of continual flux, the four predominant MCO models are as follows (Horgan 1995):

> *... the publicly funded alcoholism treatment system now serves women, adolescents, injection drug users, and individuals referred from the courts for alcohol-related offenses.*

- Managed indemnity organizations with fee-for-service structures
- HMOs—prepaid plans using specified groups of providers
- Preferred provider organizations (PPOs)—plans requiring the use of preselected providers
- Point-of-service plans—plans offering services by providers other than the primary, preselected providers, with higher cost for supplementary providers

Within this context, HMOs represented one-fifth of the privately insured population enrolled in managed care arrangements by 1993 (Group Health Association of America 1994).

Across MCOs is a trend toward "carving out" alcohol, drug, and mental health services, whereby the "*carve outs*" are characterized as services provided outside the health care organization (Mechanic et al. 1995). There is some indication that availability and types of service may differ across managed care models. For example, two studies showed that across HMOs surveyed, a substantial range in type and amount of covered services was related to such factors as ownership, type of HMO model, and HMO size (Jensen and Morrisey 1991; Levin et al. 1984).

A new organizational trend is the development, by many States, of public managed care approaches for treatment of alcohol and other drug abuse. These approaches use block grant and Medicaid funds in a variety of managed care options (Commons et al. 1994*a,b*).

During the past several years, an important organizational change has been the consolidation of many alcohol and drug treatment and prevention programs at the State and local levels. As a result, the number of programs treating problems related to both alcohol and other drug abuse has substantially increased. In the 1989 NDATUS, more than 65 percent of the 7,759 public and private programs were reported as combined alcohol and drug programs—an increase of 234 percent in 7 years (Weisner 1992). Programs for drug treatment alone decreased by 16 percent, and programs for alcoholism treatment alone decreased by 46 percent. By 1993, the proportion of combined programs had increased to 82 percent of the total (special SAMHSA analysis of the 1993 NDATUS for this report).

Financing

Funding levels and mechanisms of financing also affect the availability of alcohol health services. Based on the NDATUS, an analysis of funding between 1979 and 1989 showed that while spending increased, availability varied substantially by State (Huber et al. 1994). For example, in six of the Western States that had the highest alcohol health services expenditures per capita in 1979, public funding per capita had dropped by 19 percent by 1989. These changes were attributed to decreases in local spending and public third-party spending, such as Medicaid. Other States increased public funding, which was attributed to increased Medicaid financing of alcohol and other drug treatment. For example, New York State expanded Medicaid coverage for substance abuse services beyond Federal eligibility requirements, at the expense of passing up Federal matching funds for these individuals and services (Huber et al. 1994).

Across States overall, the public financing patterns of alcohol services do not appear to be affected either by changes in State spending or by Federal block grant mechanisms. This is partially the result of the initial distribution of the block grant funds being based on historical funding levels, with revised allocation formulas applying to incremental funding only (Huber et al. 1994). Furthermore, neither changes in mandated private insurance coverage of alcohol treatment between 1979 and 1989 nor changes in per capita alcohol consumption substantially affected public spending on treatment. In constrast, increases in real per capita income raised State and local government spending on alcohol treatment (Huber et al. 1994).

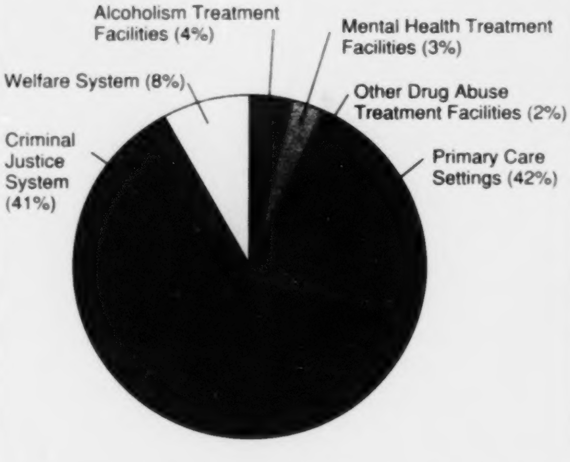
At the same time, growth in spending for treatment in the public sector has been disproportionately lower than that in the private sector (Huber et al. 1994; Schmidt and Weisner 1993). Public funds from a variety of sources (e.g., block grants and Medicaid) are distributed to private and nonprofit agencies as well as to public agencies. As a result, public funding continues to be the main source of support for alcohol health services, especially for prevention activities. Nonetheless, there is a clear distinction between funding for the treatment of alcoholism and other drug abuse versus funding for other medical treatment: For substance abuse, public funds make up 59 percent of the total costs of treatment, with 50 percent of that from Federal block grants or other State and local government funds. Private insurance contributes only about 20 percent of total funds for substance abuse treatment, whereas for general health care, it contributes about 75 percent (Rogowski 1992).

Nonalcohol Specialty Services

Rates of problem drinking are high among the clientele served by many community institutions outside the specialty alcoholism treatment system. These agencies include criminal justice, welfare, mental health, and health care agencies. For example, in one county's public sector, when problem drinker rates were adjusted to the gender, age, and ethnicity distributions in the general population (where prevalence of problem drinking was 11 percent), they represented 15 percent of patients entering public primary care institutions; 19 percent of those receiving emergency department services; 24 percent of those enrolling in welfare agencies through Aid to Families With Dependent Children and General Assistance; 26 percent of those entering mental health facilities; 54 percent of those arrested on criminal charges; and 40 percent of those being admitted to drug treatment facilities (Weisner and Schmidt 1993). In the same county, rates of problem drinkers entering HMO emergency rooms were 11 percent and were 7 percent of those entering HMO primary care settings (Weisner 1995). Figure 1 shows that when this same county is viewed in an overall context of service provision to problem drinkers, caseloads in primary care settings and the criminal justice and welfare systems carry the substantial burden for handling problem drinkers. Research has shown that most individuals entering public specialty treatment did so after having been on welfare or in jail. Problem drinkers in jail typically had not previously been in alcohol treatment (Tam et al. 1996). This is important because of issues of cost and effectiveness. Recent research has found alcohol and other drug treatment to be more effective and less expensive than a traditional criminal justice approach (e.g., incarceration) to substance abuse (Gerstein and Harwood 1990; McLellan et al. 1996).

Figure 1. Distribution of problem drinkers entering health and community agencies in one California county.*

The term "problem drinker" includes heavy drinking, social consequences, and/or dependence symptoms. Problem drinkers were identified by surveying all clients entering these agencies, using in-person interviews with structured questionnaires.



*The figure weights the problem-drinking caseload of each system to be representative of its proportion within the context of public community services.
Source: Weisner 1995.

Informal Services

Informal services such as mutual help associations and religious organizations have an important role in ensuring the availability of alcohol health services. The source of informal help most often received by problem drinkers is Alcoholics Anonymous (AA) (McCrady and Miller 1993). In fact, trend analysis of the 1990 National Alcohol Survey has shown that higher numbers of problem drinkers attend AA meetings than formal alcohol treatment programs and that this relationship remained stable from 1979 to 1990 (Weisner et al. 1995). AA is increasingly used as an adjunct to treatment or as aftercare, often with the explicit goal of providing the problem drinker with ongoing "non-drinking community support" (IOM 1990; Kaskutas and Greenfield 1995).

Access to and Use of Alcohol Treatment Services

Many of the factors that affect service availability are also important to understanding the differential access of various population groups to services and how the interaction of individual, organizational, and financing factors affect the use of the alcohol treatment system. Documentation of the incentives and barriers that influence entry into treatment can shed light on issues that affect treatment access, including the need and demand for treatment.

Understanding the need for treatment and access to alcohol health services is necessary for planning the service provision and designing mechanisms to facilitate the use of appropriate services by specific population groups (e.g., child care for single parents, culturally specific services, or satellite centers for rural areas). The ability to estimate potential levels of use in the absence of barriers is crucial in the development of treatment policy.

In examining access from the perspective of need and demand for treatment of the different population groups who use it and their special barriers and incentives, this section first describes characteristics of the clients in the national alcohol treatment system. It then summarizes the research on need and demand for services and the factors affecting access and use. A review of what is known about the treatment entry process leads to recommendations for future research.

Characteristics of the Treatment Population

Estimates of need first have to take into account existing patterns of utilization as well as changes in the characteristics of those in treatment over time. A trends analysis of NDATUS data showed that the proportion of individuals in treatment for alcoholism in the 21- to 44-year age group increased between 1982 and 1993, as it did for African Americans and women (table 2). Another analysis of NDATUS found that the number of units offering specialized services for women increased from 23 to 53 percent between 1982 and 1992 (Schmidt and Weisner 1995). Thus, from the perspective of treatment statistics, the social policy goals of increasing women's representation in treatment were begun to be met during this period.

Another perspective on use comes from studies of the general population. A trends analysis of the National Alcohol Survey—a survey of the general population of the United States conducted every 5 years—showed that

Table 2. Sociodemographic characteristics of clients in alcohol treatment programs* in 1982, 1990, and 1993 (in percentages and numbers†), National Drug and Alcoholism Treatment Utilization Surveys (NDATUS).

	1982		1990		1993	
Characteristic	**%**	**(N)**	**%**	**(N)**	**%**	**(N)**
Gender						
Men	78	(217,324)	72	(350,508)	71	(585,691)
Women	22	(62,556)	28	(136,155)	29	(236,597)
Ethnicity						
White	71	(200,830)	69	(315,772)	63	(512,270)
African American	16	(44,265)	21	94,883)	22	(179,211)
Latino	9	(26,574)	8	(34,542)	12	(96,088)
Asian	<0.5	(922)	1	(2,701)	1	(7,560)
Native American	4	(10,578)	3	(11,865)	3	(22,813)
Other	NA		NA		NA	(4,346)
Age (years)						
< 21	12	(31,846)	15	(70,485)	12	(97,657)
21–44	59	(163,807)	70	(329,621)	73	(603,059)
45–64	27	(75,735)	14	(63,486)	14	(112,478)
≥ 65	2	(6,114)	1	(5,032)	1	(9,094)

*Includes alcohol-only and alcohol and drug combined programs.
†Sample sizes (in parentheses) may vary due to missing data. Combined percentages may not sum to 100% due to rounding error.
Sources: Schmidt and Weisner 1993 (p. 351) for 1982, 1987, and 1990; a special analysis of the 1993 NDATUS by the Substance Abuse and Mental Health Services Administration for this report for 1993. Schmidt and Weisner 1993 is reprinted by permission.

between 1979 and 1990, increasing proportions of adults reported seeking help for their alcohol problems and attending specialty alcohol programs (Weisner et al. 1995). When researchers made adjustments for other demographic characteristics and the year of the survey, the analysis pointed to men and unmarried persons as the most likely to report seeking help with alcohol problems. However, it is important to point out that general population and facility-based studies of treatment use, such as NDATUS, have certain limitations. Household surveys may exclude institutionalized persons, the homeless, and persons not residing in all types of housing units. These excluded persons may have a greater likelihood of having alcohol-related problems than others in the general population (Tam et al. 1996). In contrast, facility-based statistics are limited by problems in sampling the universe of agencies, particularly private programs, and may overrepresent the very individuals less likely to be found in household surveys (National Institute on Drug Abuse 1990). General population-based studies include users and nonusers of services and make it possible to examine barriers, including attitudes, that affect nonuse of services (Aday 1993).

Among individual factors clearly related to treatment entry are gender, age, marital status, and ethnicity.

Treatment Need and Demand

Estimates of need for treatment may be based on measures of alcohol dependence, alcohol abuse, or problem drinking. The most recent NLAES data indicate that the prevalence of alcohol dependence (see the definition in chapter 9) in the U.S. adult general population was 7.4 percent in 1992 (Grant et al. 1994). However, because of interest in opportunities for prevention, as well as a national treatment focus that emphasizes early case finding, rates of "problem drinking" (as defined by IOM 1990) are often used to estimate need. Criteria for problem drinking (including heavy drinking, symptoms of dependence, and social consequences) were used in a 5-year study of stability and change in women's problem drinking (Wilsnack et al. 1991). In 1986, at 5-year followup, 37 percent of problem drinkers continued to report two or three indicators of drinking problems, and 31 percent of problem drinkers continued to report one problem indicator. Moreover, the study reported notable change in drinking behavior over a 5-year period. While 33 percent of problem drinkers were free of problems at followup, 11 percent of nonproblem drinkers reported at least one sign of problem drinking. In another study, criteria similar to those in the study by Wilsnack et al. (1991) were used to identify a problem drinking rate of 11.3 percent in the general population of a northern California county; the rates for women and men were 5 and 19 percent, respectively (Weisner and Schmidt 1992).

Demand plays an important role in determining need for alcohol treatment. Demand is shaped by social policies that target individuals for treatment. For example, laws on drinking and driving and social policies regarding welfare payments may be tied to treatment attendance. Consequently, use of alcohol treatment services is often associated with coercion, and treatment referrals may come from the criminal justice system (as an alternative to harsher legal sanctions), from the workplace, or as a result of family and community pressure (Gerstein and Harwood 1990; IOM 1990).

Alcoholism prevention and treatment programs are organized in and shaped within the context of changing issues and concerns in communities (Greenfield and Zimmerman 1993). The availability of treatment (IOM 1990), concerns about the seriousness of alcohol-related problems, and attitudes toward treatment influence demand. Decreased or stabilized alcohol use has been observed concomitant with increased concern about alcohol and alcohol-related problems in some population groups (Room et al. 1991). Increases in informal pressures on heavy and problem drinkers and tightening of norms regarding excessive drinking in many situations (Greenfield and Room in press) also are associated with increased use of treatment.

Factors Affecting Access and Use

Individual Factors

Demographic characteristics play an important role in treatment use. Among individual factors clearly related to treatment entry are gender, age, marital status, and ethnicity (Bannenberg et al. 1992; Horgan et al. 1994; Schmidt and Weisner 1993). Although investigators have not widely examined gender differences by using comparable populations and measures (Jordan and Oei 1989), study results suggest that by the time women enter treatment, they may have more severe alcohol or psychiatric symptoms than men (Farid and Clarke 1992; Weisner and Schmidt 1992). Moreover, women are less likely than men to define alcohol as their main problem (Thom 1986).

What factors predict entry into alcohol treatment? A study of individuals entering public alcohol treatment agencies and problem drinkers in the general population (Weisner 1993) showed that for women, demographic characteristics (being older; white; unmarried; and having a lower level of education, employment, and income) were the most important predictors of entry into treatment. For men, alcohol-related social consequences (e.g., arrests, serious family problems, and being talked to about alcohol problems by a health professional) and demographic characteristics (particularly being older and a member of an ethnic minority) predicted treatment entry. This was a study of the public treatment system and thus did not address the role of income and insurance coverage. An analysis of treatment entry from the 1992 NLAES general population survey found that among individuals who were alcohol dependent, those who had been to treatment were younger, had lower educational levels and incomes, and higher levels of severity than those who had not (Grant 1996).

One of the most dramatic developments in the organization of alcohol treatment has been the growing use of managed care to contain costs by restricting unnecessary treatment.

Other studies have shown that patterns of treatment use vary by age. For example, older adults (aged 65 and older) are more often hospitalized (Adams et al. 1993). In another study, older adults (55 and older) received less specialized inpatient or outpatient treatment for their substance abuse or psychiatric problems than their younger counterparts. Instead, older patients received medical management rather than rehabilitative substance abuse or psychiatric treatment (Moos et al. 1993).

Utilization of alcohol health services is not equal across ethnic groups. National data show that the percentage of Hispanics in public alcohol treatment programs is lower than their problem drinking rates in the general population, except in programs serving as legal sanctions for drinking and driving. At the same time, the percentage of African Americans in public treatment programs is higher than the proportion of problem drinking African Americans in the general population (NIAAA 1990; Weisner and Schmidt 1993). Other research has shown that socioeconomic status is an important confounder in the examination of problem drinking among African Americans. Socioeconomic status was an important predictor of levels of problem drinking when race was controlled for; drinking levels were related to education, for example, rather than race (Barr et al. 1993), and may explain the overrepresentation of African Americans in some agency systems. Because of differences in services offered by the public and private sectors (Yahr 1988), the overrepresentation of African Americans in public treatment may indicate that they have less access to the full range of services (Gerstein and Harwood 1990; Gilbert and Cervantes 1986; IOM 1990).

Finally, use of treatment services is influenced by differences by ethnicity in health beliefs that trigger treatment seeking as well as barriers (Bardsley and Beckman 1988). Although the national treatment statistics discussed above have not shown increased representation of Hispanics and Asian Americans in alcohol treatment facilities, some studies have found an increased prevalence of both alcohol problems and barriers to treatment for these groups (Estrada et al. 1990; Gilbert and Cervantes 1986, 1988; Ja and Aoki 1993).

Organization-Level Factors

In the current environment of changing health care policy, various models of managed care are important research topics. Investigations of how services are organized and administered at the agency and systems levels compare dominant organizational characteristics, such as managed care and traditional private indemnity, fee-for-service programs, and types of MCOs (Mechanic et al. 1995). These studies focus on mechanisms used across organizations (e.g., utilization review and case management) and on issues of interorganizational access that cut across both health and social service (e.g., welfare and criminal justice) systems.

One of the most dramatic developments in the organization of alcohol treatment has been the growing use of managed care to contain costs by restricting unnecessary treatment. Broadly defined, managed care programs are designed "to control access to care, types of care delivered, or the amount/costs of care" (Wells et al. 1995, p. 57). One approach to the study of MCOs (Mechanic et al. 1995) groups them into categories of prepaid health plans (often HMOs), in which providers are given a set amount of dollars to cover health care for each member; utilization management by third-party organizations whereby each treatment episode is reviewed for its *appropriateness* and proposed length of stay (or number of visits); and case management whereby treatment need and placement are coordinated by a third party. Each type of management may influence organizational behavior and affect access in a different way, mostly due to its cost-containment mechanisms. These categories can be subdivided further by budget constraints used to control health services costs (e.g., fixed budgets or *capitation*), financial incentives for providers (e.g., reduction of provider incomes when more services are used), and review of treatment plans against criteria defining appropriate care (Mechanic et al. 1995).

Although managed care arrangements initially involved only private treatment for alcoholism, State and county systems and public insurance have increasingly adopted similar mechanisms to improve economic efficiency in the delivery of services; these mechanisms include HMOs, PPOs, selective contracting, utilization review, and case-monitoring strategies (Clark and Fox 1993; Keeler et al. 1988; Rogowski 1992; Tischler 1990; Wells et al. 1991). Few formal controls are used to govern MCOs and to ensure that cost-containment efforts do not hamper accessibility or affect the quality of service (Borenstein 1990; England and Vaccaro 1991).

Group practices most frequently have used financial incentives to discourage use of services and of particular treatment modalities; *independent practice associations* (IPAs) have used various designs of benefits and incremental *copayments* to discourage such use (Altman and Goldstein 1988). Within the context of treatment access and barriers, HMO model types influenced the length of waiting time for patient intake (which may discourage patient access to and use of services). With initial appointments provided within a week of initial patient contact, IPAs were more consistently responsive to patient demand for substance abuse treatment than staff or group practices, which had waiting periods that ranged from days to more than 6 weeks.

The Shift From Inpatient to Outpatient Services

Within alcohol treatment agencies, the proportion of outpatient units more than doubled between 1982 and 1990 (Schmidt and Weisner 1993). This increase was consistent with a major focus on MCO efforts to decrease utilization of inpatient services. The dominant organizational results of the focus on cost containment during the past 10 years may have been shorter duration inpatient programs; a substantial shift to outpatient programs as the predominant treatment setting; and an increase in nonmedical approaches, such as halfway houses and other nonmedical residential programs. Some earlier studies had indicated that prospective payment systems often provide financial incentives weighted in favor of a general hospital model emphasizing brief-stay detoxification and outpatient treatment (Mezochow et al. 1987). One evaluation of this potential service shift versus overall service loss in a prepaid MCO showed that as the use of short-term detoxification programs increased over time, inpatient services decreased, but there was no concomitant increase in outpatient treatment (Thompson et al. 1992).

After their adoption of managed care plans for the provision of mental health services, several States have examined access to these services in terms of the number of inpatient and outpatient admissions. Although inpatient admissions and costs were consistently lower for MCOs compared with unmanaged fee-for-service insurance, mental health service admissions varied across States (Mechanic et al. 1995). In evaluations of capitation experiments in Minnesota, New York, and Utah, greater differences were found for outpatient mental health services for alcohol and other drug abuse than for inpatient services. For example, New York's capitation program had the largest reduction in hospitalization as well as the largest increase in the use of outpatient services. In other States, however, analysis of first-year utilization rates revealed that decreases in outpatient services accompanied decreases in inpatient services. There is a strong likelihood that similar results would be found for substance abuse (see studies reviewed in Mechanic et al. 1995).

Mechanisms Used To Manage Care

Utilization review is a mechanism commonly used to contain costs via case-by-case assessment of the amount and type of care. In a study of 1984–1985 records for general health care services, researchers found cost reduction in all areas (admissions, inpatient days, hospital expenditures, and total medical expenditures) associated with utilization review (Feldstein et al. 1988). More specifically related to alcohol and other drug abuse treatment, as well as other mental health services, Hodgkin (1992) found that utilization review neither improved nor substantially disrupted services. In another study of utilization review of alcohol and substance abuse treatment services, predominant savings appeared to result from a reduction in inpatient services; however, as with prepaid mechanisms, these reductions were not accompanied by increases in outpatient services (Mechanic et al. 1995). These studies, however, have not examined the impact of decreased costs on treatment outcomes for alcohol and other drug abuse services.

In developing a utilization review approach for its Medicaid program, the State of Massachusetts has used a PPO network to contract with many preexisting service providers. Evaluation of the results of this utilization review (Mechanic et al. 1995) showed a substantial drop in inpatient services for substance abuse. Although there was no concomitant increase in use of outpatient services for substance abuse, the use of lower cost types of residential treatment increased.

The Massachusetts managed care program initially focused on diverting men and women seeking detoxification and rehabilitation services in acute care hospitals to freestanding detoxification centers. Assessment of the program revealed substantial savings during the first year and increased access to all levels of care except hospital services. At the same time, the cost of services for treatment of alcohol abuse and other drug abuse decreased (Callahan et al. 1994).

Case management is another strategy that has been used to control costs. Different case management models include those in which case managers assess patient needs and strengths and link them to existing health and social services, and those in which case managers link patient needs and strengths to health and social services and also provide these services, such as money management (Clark and Fox 1993). Case management has a longer history of use in the mental health than in the substance abuse field and as a strategy to control cost, and has had mixed results according to early evaluations of mental health and substance abuse programs (Mechanic et al. 1995). Whereas earlier programs focused on the public sector, this approach has begun to be used in the private sector as well. In early studies, for example, one large corporation reported decreased service costs accompanied by decreases in absenteeism and job turnover; another study of 25 businesses showed no cost reductions due to decreases in either hospital readmission rates or long durations of stay (Mechanic et al. 1995). Case management has often been used with individuals who have a range of severe mental health and substance abuse problems, and researchers examining the cost-effectiveness of case management point out that the type of treatment model, client characteristics, and characteristics of available treatment resources and support services available must be especially considered in such evaluations (Clark et al. 1993).

Changes in the relationships between alcohol treatment systems and other health and social service systems have important implications for access to treatment. For example, increasing legal sanctions for alcohol and other drug-related offenses during the 1980s led to a disproportionate increase in alcohol and other drug abusers in criminal justice settings (Mauer 1992; U.S. Bureau of Justice Statistics 1991). The interorganizational response was an increase in referrals to alcohol treatment programs from the criminal justice system; the number of referrals raised concerns about the policy's effect on access for clients who were not referred by the criminal justice system (IOM 1990). There is no indication from the NDATUS or other similar surveys that the supply of services has increased to provide treatment for this new group as well as traditional clients (Schmidt and Weisner 1993). This lack of an increase in capacity has caused concern among many in the field about the allocation of scarce public treatment resources.

Some States and local jurisdictions still lack clearly defined dispositional rules for multiple offenders convicted under laws against drinking and driving; the absence of such rules leads to very different referral patterns. One study showed that sentences which involved alcohol treatment appeared to be related more to fiscal factors, jail overcrowding, and ideological orientations than to problem severity (Speiglman 1994).

Financing and Reimbursement Factors Influencing Access

Alcohol health services research also examines the financing of treatment services and the effects of different financing patterns on type and amount of services and use. Like the field of general medicine, the alcohol treatment field has extremely fragmented financial and reimbursement systems that are not integrated even in terms of an overall reporting system. Thus, tracking the extent and patterning of changes and their effects on the service system is difficult.

As containment of health care costs has become a national economic priority, significant changes have occurred in the financing of alcohol treatment and prevention services. Although increasing numbers of

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people in the United States do not have health care coverage, the public sector has not kept pace with private sector growth to be responsive to those needs for alcohol and substance abuse services (Huber et al. 1994). These funding shifts imply reduced access for the public client (Schmidt and Weisner 1993), a group that is most at risk for having alcohol problems (IOM 1990). At the same time, however, a larger proportion of those who have third-party health insurance have alcohol and drug treatment as part of that coverage (Jensen and Morrisey 1991; Kronson 1991). This increased availability is a significant improvement.

A study of outpatient substance abuse units showed that public programs turned away fewer clients than private programs did. Public programs had larger numbers of clients on waiting lists for more days, more clients paying reduced fees, and more clients unable to pay than did private nonprofit programs. Private for-profit programs had the least number of clients in each of these three categories, and they turned away more clients (Wheeler et al. 1992). It will be important to examine whether patients were turned away due to inability to pay, for lack of diagnostic eligibility for the program, or for other reasons.

The 1988 Employee Benefits Survey of the U.S. Bureau of Labor Statistics represents the 106,000 nongovernment firms with 100 or more workers. The survey showed that 90 percent of workers had general medical insurance and 81 percent had coverage for the treatment of alcohol abuse and dependence (Jensen and Morrisey 1991). In 1989, a similar study using this survey showed that 97 percent had coverage for alcoholism treatment (Kronson 1991). However, the picture of access by type of alcohol treatment services differs somewhat. Although each of the insurance plans covered inpatient detoxification, only 68 percent covered inpatient rehabilitation and only 61 percent covered outpatient care. Furthermore, 44 percent of fee-for-service and HMO plans with inpatient coverage had limited days of treatment. HMOs allowed more inpatient and outpatient days for alcohol-related treatment per year but fewer per episode and lifetime (Kronson 1991). Thus, despite the pervasiveness of third-party coverage for alcohol treatment services, it is characterized across the board by various limitations, especially in the numbers of inpatient days and outpatient visits per year (Jensen and Morrisey 1991).

Public Versus Private Funding

State policies oriented toward containing costs and reforming the health care system have altered access to services for both public-sector (e.g., Medicaid-Medicare) and private-sector insurance (Freiman et al. 1987; McGuire et al. 1987; Mitchell et al. 1987). For example, the DRG approach to regulating Medicare reimbursements has resulted in reduction in general mental health expenditures, although this reduction is generally achieved by decreasing durations of hospital stay and inpatient bed days (McGuire et al. 1987). Indeed, most health care policy changes have affected the public sector as well as the private sector.

States are now focusing on integration of Medicaid funds into their public managed care programs. On the whole, Medicaid has not been a prominent payer for services for alcohol abuse and other drug abuse because its medical model does not always fit alcohol treatment services, and the Federal and State relationships in Medicaid reimbursement policy are complex (Horgan et al. 1994). In a study of two States, Wright and Buck (1991) found that 9 to 10 percent of Medicaid patients received substance abuse services; that costs made up 22 percent of total Medicaid payments; and that expenses for alcohol, other drug, and mental health services were 11 to 12 percent of overall Medicaid costs. Other studies have indicated that the population groups with the highest prevalence and severity of substance abuse problems, especially single men and women without children, are often unable to access services through Medicaid (Rosenbach and Huber 1994).

A recent study (Lo and Woodward 1993) showed that Medicare costs for alcoholism treatment are lower because of a lower average duration of hospital stay, lower monthly health expenditures, and a subsequent reduction in use of health care services when services are provided by freestanding facilities rather than hospitals. Taking into account both publicly and privately funded organizations, Huber et al. (1994) determined that access to services is far from consistent from State to State. Wright and Buck (1991) found that Medicaid substance abuse services varied across the States they studied, especially in terms of inpatient and ambulatory services.

Despite concern that the mandating of insurance benefits to cover alcohol and other drug abuse treatment by States would have a negative effect on access to these services, a study of six States (Browne et al. 1987) showed that those fears were unfounded. No substantial increases in insurance premiums, changes toward self-insurance, or termination of plans could be connected to mandating these benefits. Although outpatient costs increased, inpatient costs decreased to the extent that the net effect of the mandated benefits was an overall decrease in outpatient and inpatient costs.

Funding Mechanisms and Access

Recent research has begun to characterize financial barriers to receiving alcohol treatment services. Researchers have examined the types of barriers associated with different financing models, including higher cost sharing by the patient to decrease the probability that a treatment will be used. Two examples are private indemnity plan deductibles and the HMO requirement for copayments rather than setting maximum payment limits, to discourage overuse of outpatient care (Kronson 1991; Rogowski 1992). HMO and private indemnity programs often use lifetime limits as well as caps on inpatient days and outpatient visits (Kronson 1991; Ridgely et al. 1990).

A fundamental issue affecting access to treatment is the distinction between carved-out services and integrated plans. Although the carve-out mechanism is becoming a predominant approach for mental health and substance abuse treatment (Freeman and Trabin 1995), it has not yet become a primary focus of research on access. A recent study of contracting mental health services showed important differences between the practices of public and private agencies but no evidence of these practices being related to differential access of low-income clients to services (Clark et al. 1994). Intervening factors, especially competition between treatment organizations, appeared to affect the role of ownership in predicting practices.

Costs and Cost-Effectiveness of Alcohol Health Services

In addition to the effect that patterns of financing of alcohol services has on access is the impact of cost. Alcohol health services research addresses four important cost issues:

1. The wide range of alcohol abuse and alcoholism-related costs to individuals and society
2. The costs of providing treatment in both the alcohol services system and other health and social service agencies
3. The health care costs that are reduced by the provision of substance abuse treatment
4. The overall cost-effectiveness of providing such treatment

Until recently, researchers in alcohol health services or other medical areas placed little emphasis on these issues. Studies and methods are being developed to address new models of care; outcome and cost for these new models are unknown. Research on matching treatment to individual need, on treatment effectiveness, and on evaluation of different organizational systems for structuring of treatment will provide a basis for configuring future services and establishing priorities for insurance coverage.

National policy development and resource allocation for research, training, treatment, control, and prevention of alcohol abuse and alcoholism require good estimates of the multifaceted effects of alcohol. The cost in dollars of alcohol health services and the loss of productivity and other related problems associated with alcohol abuse, such as accidents and crime, represents a point from which to begin assessing the real effects of alcohol abuse and its consequences for society.

Economic Costs to the Nation

Measuring the economic toll of alcohol abuse is inherently fraught with methodological and conceptual difficulties. Differences in components of cost, data sources, estimation procedures, and discount rates have led to considerable variation in the numbers that represent the national economic burden attributable to alcohol. The annual cost was estimated to be as high as $116,674 million in 1983 (Harwood et al. 1984) and as low as $70,338 million in 1985 (Rice et al. 1991). The 1985 estimate served as a starting point from which to develop projections for 1990; Rice (1993) analyzed data on costs of alcohol abuse using socioeconomic indexes to determine the 1990 adjustments for that year (Rice 1993). Simple linear extrapolation from the 1985 and 1990 totals suggests an estimate of $125 billion for 1995. However, this estimate does not take into account the unprecedented changes in the Nation's health care system during the past decade (Huber et al. 1994; Schmidt and Weisner 1993).

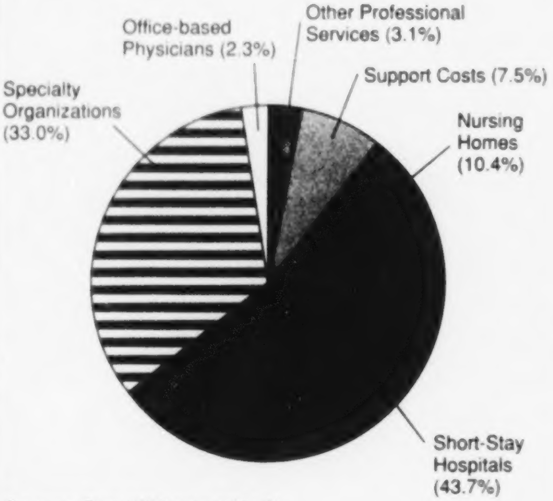
The 1985 and 1990 estimates shown in table 3 represent systematic analyses of data drawn from many national sources. In addition to the direct costs of health care and associated medical support (number of services

Table 3. Estimated costs of alcohol abuse, 1985 and 1990.

Type of Cost	1985[*] Amount in Millions	1990[†] Amount in Millions	1990[†] Percent Distribution
Total	$70,338	$98,623	100.0
Core Costs	58,181	80,763	81.9
Direct Costs	6,810	10,512	10.7
Specialty organizations	2,281	3,469	3.5
Short-stay hospitals	3,017	4,589	4.7
Office-based physicians	141	240	0.2
Other professional services	173	329	0.3
Nursing homes	703	1,095	1.1
Support costs	495	790	0.8
Indirect Costs	51,371	70,251	71.2
Morbidity	27,388	36,627	37.1
Noninstitutionalized population	27,208	36,404	36.9
Institutionalized population	180	223	0.2
Mortality[‡]	23,983	33,624	34.1
Other Related Costs	10,546	15,771	16.0
Direct Costs	7,380	10,436	10.6
Crime	4,251	5,807	5.9
Motor vehicle crashes	2,584	3,876	3.9
Fire destruction	457	633	0.6
Social welfare administration	88	120	0.1
Indirect Costs	3,166	5,335	5.4
Victims of crime	465	576	0.6
Incarceration	2,701	4,759	4.8
Special Diseases			
Fetal alcohol syndrome	1,611	2,089	2.1

[*] Rice et al. 1990.
[†] 1990 costs are based on socioeconomic indexes applied to 1985 estimates.
[‡] Discounted at 6 percent.
Source: Rice 1993.

Figure 2. Direct core economic costs of alcohol abuse in 1990.

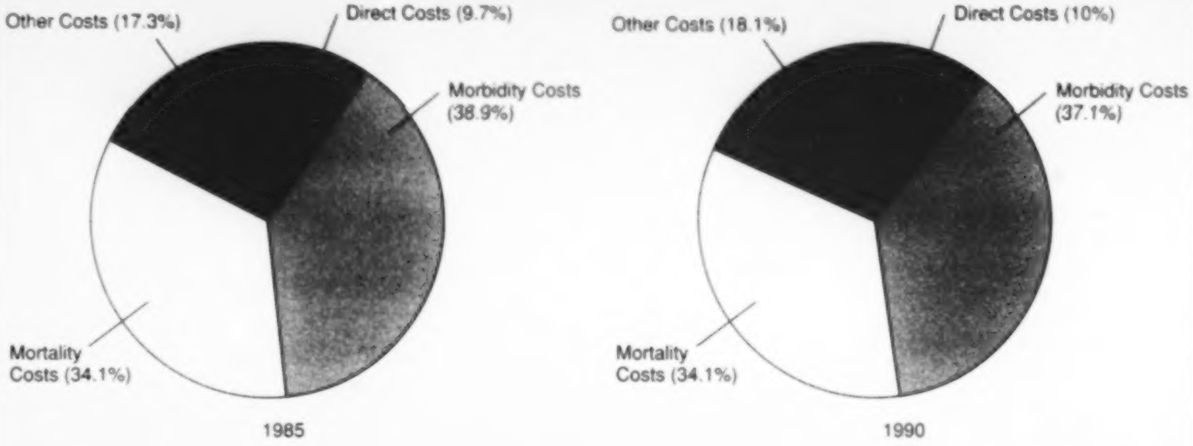


Source: Rice 1993 (see table 3).

multiplied by unit charges), the core costs shown in the table include the indirect costs of morbidity (lost productivity as a percentage of loss due to alcoholism multiplied by an individual's expected average income without alcoholism) and mortality (the value of loss due to premature death, presented as discounted future earnings). Other related nonmedical costs include the direct costs of crime, accidents (e.g., motor vehicle crashes and fires), and social welfare administration, and indirect costs such as lost homemaker and caregiving services (the value of time spent) and the crime-related costs of victimization and incarceration.

These estimates provide a useful overview. The breakdown of direct core medical expenditures (totaling $10.5 billion in 1990) represented as percentages in figure 2 is based on those projections and amounts to approximately 11 percent of the annual cost of alcohol abuse (see table 3). The largest share (more than three-fourths) of the total direct medical service cost (approximately $8.1 billion in 1990) represents

Figure 3. Economic costs of alcohol abuse by type of cost, 1985 and 1990.



Sources: Rice et al. 1990; Rice 1993 (see table 3).

expenditures for specialty treatment short-stay hospitalizations. Also broken out of the total economic burden for 1985 shown in table 3 are costs for fetal alcohol syndrome—approximately $1.6 billion.

Striking among the policy-relevant statistics included in this picture of the cost of alcohol abuse (Rice et al. 1991) is the cost of alcohol-related mortality: $24 billion in 1985 as estimated from lost productivity (see table 3 and percentages in figure 3). Individuals aged 15 to 44 years old accounted for 36 percent of those dying from alcohol abuse, for 59 percent of the person-years lost, and for 71 percent ($17 billion) of the total mortality costs ($24 billion) in 1985 (Rice et al. 1990). Reflecting the prevalence of alcohol use (Midanik and Clark 1994), problems (Midanik and Clark 1995), and dependence (Grant et al. 1991) in this age group, mortality accounts for 60 percent of alcohol-related core health system costs, 81 percent of which are attributable to males.

These estimates are conservative. On one hand, they omit the costs of handling alcohol use disorders as well as the mortality and morbidity productivity losses of homeless and military populations. On the other hand, they are important for juxtaposing the costs associated with alcohol-related crime, estimated for 1990 to account for $11 billion or 11 percent of the total cost of alcohol problems in the United States, and the approximately equal cost of alcohol-related core health care services.

Costs of Alcohol Health Services

Within these societal costs, a substantial portion involves costs associated with specialty treatment of alcohol use disorders and care of alcohol-related medical consequences. Also included in the cost of treatment services are service delivery costs (e.g., staff and equipment), private costs to persons receiving treatment (e.g., out-of-pocket costs, lost productivity during treatment, and transportation and child care costs), and social costs (e.g., Medicaid payments).

Most studies assessing alcoholism treatment costs use charges or actual expenditures. Research varies, however, with regard to whether the data represent actual costs or the charges of service providers. Estimates based on data on charges, which often rely on DRG prices, have limited value because they may be higher than true costs; in other words, they may include charges that represent strategies to maximize revenue. Another concern is that the Medicare cost report on which charges are based has not been reliable across hospitals and studies (Newhouse et al. 1989). Moreover, isolating alcohol-related costs can be difficult, given the high prevalence of comorbid conditions (e.g., alcoholism co-occurring with mental disorders).

The growth of MCOs signals the need for new methods of estimating costs under the various arrangements in which fees are not paid by unit of service. Estimates of the units of service required for each potential admission are calculated on the basis of estimated numbers of potential clients. Because many

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MCOs simply record use averages, rather than costs per individual or costs per service, researchers need to develop more accurate methods of estimating the units of service required by individual clients across different organizational models.

Data for Measuring Costs

The IOM (1990) report on alcohol treatment emphasized concern about the lack of comparable data on costs of treatment across funding sources. Among numerous sources of data for cost estimation is the NDATUS described earlier, which is a repository of data on program-level funding. Another source is the State Alcohol and Drug Abuse Profile, which includes data collected by States on the characteristics of clients and programs receiving public funds. In addition, data collected by the American Hospital Association covers charges for alcohol treatment in hospital settings. Use of these data systems to estimate costs is complicated by the spectrum of organizations and settings providing treatment. The services range from non-medical-based clinics and hospitals to detoxification and outpatient services and halfway houses. In addition, although data from these sources provide a means to compare estimated costs, definitions of cost and unit of services vary among States, and real-cost data are usually unavailable.

For the past few years, insurance claims data (e.g., private insurance claims and Medicare claims data) have been used to estimate costs of alcoholism treatment. There is some concern about comparability of definitions and data across plans; however, insurance data are representative of individual clients and provide opportunities for researching cost, although they are based on charges rather than actual cost. Data needed to estimate participant or social costs usually come from consumer surveys. These surveys also provide important cost information, but yield conservatively biased cost estimates.

Treatment Costs

Much of the research on alcoholism treatment costs was summarized in the 1993 *Eighth Special Report to the U.S. Congress on Alcohol and Health* (in chapter 11). A recent study of self-insured individuals in the private sector (Garnick et al. 1994) showed that charges for behavioral health care average $25 per person per year. This study confirms earlier work indicating that alcohol treatment charges are higher for inpatients than for outpatients and higher for hospital-based inpatient treatment than for treatment delivered in nonhospital residential settings (Harwood et al. 1984; Holder and Blose 1991). A study that demonstrated different costs by treatment setting (inpatient versus outpatient) also documented the impact of comorbidities on treatment location and cost (Goodman et al. 1992). Psychiatric and drug comorbidities increased the likelihood of placement in a more costly treatment location (i.e., an inpatient setting); however, once treatment placement occurred, comorbidities had little impact on differences in charges for outpatient or inpatient services.

Researchers also have begun to investigate the costs of alcohol use and other drug abuse to Medicaid. Analysis of data from the National Hospital Discharge Survey showed that in 1991, the expenditure for 5.3 million days of care (20 percent of all days of hospitalization covered by Medicaid) was $4 billion. Eighteen percent of that amount was spent on alcohol-related cases, 41 percent each for cases involving tobacco and other drugs (Fox et al. 1995). Of the 5.3 million days of care, 4 million were for associated medical conditions, rather than conditions fully attributable to the abuse of alcohol or other drugs. This result was expected in that the study focused on hospital care, excluding the range of nonhospital services that provide alcohol and other drug treatment.

Other costs that should be tracked are associated with nonspecialty providers, such as those in the general medical sector, welfare, voluntary social services, mental health, and criminal justice agencies, that respond to alcohol and other drug problems. Tracking these costs is important, in that cost shifting occurs when access to one system is limited. For example, costs may be much higher to the welfare or criminal justice system when alcoholism services are limited. Although no empirical studies on such cost shifting have taken place, the area warrants further investigation. Assessments of cost-containment mechanisms, in this case in regard to utilization review, should not accept net cost reductions of medical services as a given because they do not take into account the cost shifting that occurs to patients and the community (Mechanic et al. 1995).

Cost Offsets, Cost-Effectiveness, and Cost-Benefit Analysis

The *Eighth Special Report to the U.S. Congress on Alcohol and Health* emphasized the positive effects of treatment on health expenditures and compared the use of alcohol health services as well as the costs of health care before and after treatment. Several comprehensive studies and reviews (Holder and Blose 1992; Holder et al. 1991, 1992) have shown that health care costs for individuals who enter alcohol treatment are higher than those for others and that these costs are lower after treatment. Related work has shown that families of individuals with alcoholism also have increased use of health care services (Holder et al. 1992).

Cost offsets and cost-effectiveness involve different but overlapping issues. From a perspective of cost offset, the fundamental objective of a program is cost savings, whereas in a cost-effectiveness approach, both the costs and the program's demonstrated effectiveness from health and behavioral standpoints are addressed without regard to saving money.

Cost offset alone may not be a realistic social policy goal or a criterion for development of health care policy, but the concept is very much a part of practical decision-making and long-range planning. For example, the decision not to fund potentially high-cost services for the treatment of alcohol abuse problems can have significant ramifications because of the probability that as such problems worsen, the eventual result will be much higher costs; for example, costs needed to cover other alcohol-related health conditions, accidents, and crime (Fox et al. 1995).

Brief motivational counseling is the most cost-effective treatment and aversion therapy and residential-milieu therapy are the least cost-effective.

Whether services are cost-effective is a fundamental question for alcohol health services research. In this era of cost containment, decisionmakers who choose which programs should receive increasingly scarce resources need to consider the effectiveness and the costs of services. The key question concerns which alcohol treatment modalities are most effective for the least cost (Holder et al. 1991).

Analysis of cost-effectiveness relates the cost of a given alcohol intervention to a specific, measurable outcome. For example, a cost-effectiveness study might compare the costs of two equally effective programs in terms of additional quality-adjusted life years gained or the cost per additional unit of improved health status.

Another method, cost benefit analysis, can provide direct comparison of a program's dollar benefit with its costs. Zarkin et al. (1994) have developed a framework that is being used in some current alcohol studies. The approach requires the designation of dollar values to outcomes, often based on a "willingness to pay" for a particular change in health status. While it can be problematic to assign monetary values to change in health status, some approaches are being developed based on the use of indirect or nonmarket techniques (French et al. 1996) as well as on strategies that were originally based on human capital and cost of illness methods (see, for example, Kenkel 1994). Because of the many different approaches being developed to examine the economic issues in this and other health areas, a U.S. Public Health Service-appointed expert panel has examined the scientific issues regarding economic evaluation approaches and suggested areas of methodological standardization to allow for comparison across studies (Gold et al. 1996).

Relatively few studies have addressed the cost-effectiveness of alcohol services directly. Recent literature reviews (Finney and Monahan 1996; Holder et al. 1992) have noted the importance of including cost-offset studies in future research agendas. Meta-analyses of research data on the overall cost-effectiveness of alcohol treatment, as well as data from field experiments of inpatient versus outpatient treatment, are discussed in the following paragraphs. These studies may help address the issues of cost and outcome as they apply to cost-effectiveness and cost offset for the future.

Overall Cost-Effectiveness

Most studies that provide information on the cost of alcohol treatment have collected data from health insurance organizations and employed persons whose problems may not necessarily represent the most severe alcohol-related problems (IOM 1990). Recently, meta-analyses of studies have begun to provide a broader picture of cost and effectiveness. Holder et al. (1991) performed a meta-analysis of evidence from studies representing 33 treatment modalities (e.g., brief motivational counseling, psychotherapy, therapy in a residential milieu, and self-help). The studies were arrayed by cost (high to low) and effectiveness (high to low). The results of this meta-analysis suggested that brief motivational counseling is the most cost-effective treatment and that aversion therapy and residential-milieu therapy are the least cost-effective. However, more recent analysis of the same set of studies, using a different approach, suggests a lack of relationship between cost and effectiveness, as well as different ranking of effective treatments. Furthermore, the observed cost-effectiveness of particular interventions may be confounded by the population served, in that the inexpensive and effective treatment studied may have been more used by individuals with less severe alcohol problems and better prognoses (Finney and

Monahan 1996; Howard 1993). These results highlight the need to consider patient subgroups when developing estimates of cost-effectiveness.

Cost-Effectiveness of Inpatient Versus Outpatient Treatment

A second line of research that sheds some light on cost-effectiveness comes from an extensive body of literature comparing inpatient and outpatient treatment for alcoholism (IOM 1990; Longabaugh et al. 1983; Saxe et al. 1983). Generally, outpatient treatment is considered more cost-effective than inpatient treatment, a conclusion that is based on evidence that lower cost outpatient treatment is at least as effective as high-cost inpatient treatment. Recent studies have generally confirmed this trend, although issues such as treatment intensity have not always been considered. In a landmark study of treatment effectiveness, Walsh et al. (1991) studied patients who were randomly assigned to either inpatient treatment, AA, or a choice of the two. The researchers found that inpatient treatment was more effective than AA on seven outcome measures of drinking. AA, despite being free, was only slightly less costly (10 percent) after 2 years than inpatient treatment. The authors attributed this to the fact that considerably more individuals assigned to AA eventually required inpatient treatment.

McKay et al. (1994) found that patients who qualified for inpatient treatment on the basis of standardized criteria (the Cleveland Level of Care Criteria) but were placed in a day-treatment program did as well as patients who did not meet the criteria for inpatient placement. Even patients who were more severely disabled fared well in the less expensive treatment setting. Because comparing inpatient and outpatient treatment can be exceedingly complex, conclusions about the cost-effectiveness of outpatient treatment should be interpreted in the context of other studies.

> *Researchers found that inpatient treatment was more effective than AA on seven outcome measures of drinking.*

Among many promising lines of research to address cost-effectiveness issues, this subfield of alcohol health services research requires further development. Researchers also need to elucidate the measurement of treatment costs (indirect versus direct costs, accounting versus economic costs, and marginal versus average costs) and take these various costs into account.

Health Services Prevention

Although health services are commonly considered in clinical and treatment contexts, NIAAA has included prevention within this framework, signifying its importance in the alcohol research scheme. There is precedent for the inclusion of prevention as a part of health services (Office of Technology Assessment 1993). Many health services research studies have appropriately examined the delivery of prevention-related services, generally to whole populations, communities, or groups, rather than to the individual.

The alcohol health services focus in the prevention field addresses activities that affect the use of specialty alcohol treatment, medical, and social services. Chapter 9 contains an overview of the status of prevention services and their effectiveness, as demonstrated in health service-oriented studies. The following discussion presents the status of alcohol-related prevention research within the broader field of health services research.

The Context of Prevention and Health Services

Prevention services usually occur within the context of educational, social, and community organizations and focus on education, public awareness, and strategies for environmental change. Screening and brief intervention programs conducted in health care, criminal justice, school, welfare, and other settings have the potential to identify problems earlier and decrease the probability of need for more extensive services in the future (see chapter 9). Burgeoning employee assistance programs and other workplace alcohol health services have emphasized prevention health services. Like early case finding and intervention, basic prevention is addressed in some of these workplace programs (Ames 1993; Janes and Ames 1993; Roman and Blum 1993).

Assessing the Costs and Effectiveness of Prevention Activities

Remarkably few cost-benefit or cost-effectiveness studies in the prevention area are based on formal quantitative methods. Most cost-benefit studies have concentrated on measuring the cost of screening (Tolley and Rowland 1991); however, other strategies for analyzing costs and effectiveness of prevention services have been suggested (Teutsch 1992). Whether such services should be required to have cost offsets beyond a simple requirement that they be effective may become an important issue.

Studies of prevention effectiveness must frequently rely on quasi-experimental or naturalistic designs, which require more cautious interpretation of conclusions than do fully randomized or controlled designs (Greenfield 1994). However, such studies, when undertaken on a reasonably large scale, are inherently "applicable to the real world" and may present fewer problems of external validity than carefully controlled efficacy studies.

It is critical to maintain the balance between treatment (interventions aimed at remediation in a person with a defined disability or condition) and prevention (interventions aimed at averting development of that disability or condition or secondary prevention, detection, and early interventions aimed at averting a more severe disorder). Health service researchers are just beginning to consider how to optimize resources across prevention and treatment (Edwards et al. 1994; Holder 1994) and are working from an increasingly stronger scientific base as discussed in chapter 9.

A key issue related to changing health care policy pertains to funding of prevention programs: There is no strong tradition of insurance coverage for prevention activities. Much of the funding for activities aimed at preventing substance abuse has been through the ADAMHA block grant mechanism, as well as other State and local public health funds. It is important to payers that savings from prevention activities are oriented toward the future. However, at least one study, which addressed hospital costs for Medicaid, has documented substantial short-term cost savings associated with prevention and early intervention programs, such as those directed toward trauma, acquired immunodeficiency syndrome (AIDS), and the effects of fetal alcohol exposure (Fox et al. 1995).

Summary

Although important work in the area of health services research was funded under epidemiology, clinical, and prevention auspices since early in NIAAA's history, there has been a concerted effort over the past few years to bring research on treatment and prevention services into the practice and policy environment. Combining its own objectives of examining the influence of individual, organizational, and financing factors on access and cost-effectiveness of care with the objective of applying basic research findings to real-world settings, alcohol health services research has evolved into a highly relevant and rigorous scientific area within NIAAA's larger research agenda.

Research on alcohol-related treatment and prevention services is taking place within a context of dramatic shifts in the organization and financing of health care in general. Although these changes have occurred throughout the history of the treatment system, no other era has faced the fundamental transformations currently occurring. This state of flux presents difficult methodological and theoretical challenges to alcohol health services research. Most of the published research is based on work conducted prior to many of these changes and provides important baseline information by which to assess new systems of care. A larger body of studies funded more recently will provide answers to important unanswered questions.

Many such questions focus on availability and access to care. Although research on the treatment system prior to the recent changes in health policy has documented the uneven access to treatment and the range of treatment services for individuals with and without health insurance, the initial studies on managed care approaches to the provision of health care in general, as well as alcohol services, have raised further questions about access.

A great deal of evidence over the years has shown that alcoholism treatment and prevention services are effective and can offset other health and social costs. Important new strategies for the treatment and prevention of alcoholism are continually being developed, including strategies using medications that can further increase the effectiveness of these services. The ongoing effectiveness of these services must be monitored within different organizational and financing contexts. As organizations for alcohol treatment continue to change, it will be important to conduct cost and effectiveness research that can inform the development of program and client-level indicators of performance and quality improvement.

The research agenda for alcohol health services also must include an examination of how well each type of managed care organization addresses the overall health and alcohol treatment needs of the individuals each covers. For example, researchers should examine the provision of appropriate cost-effective services and access to those services. Researchers also need to examine the cost issues of changes in the provision of alcoholism treatment services within a larger economic context of potential cost-shifting to other health care needs, such as tuberculosis, AIDS, and birth defects, as well as to other social systems, such as the criminal justice system.

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NIH Publication No. 97-4017
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism
Printed 1997

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